ANNUAL REPORT
OF
PROGRAM ACTIVITIES

NATIONAL INSTITUTES OF HEALTH

1967 - 1968

DIVISION OF COMPUTER
RESEARCH AND TECHNOLOGY
DIVISION OF RESEARCH SERVICES
DIVISION OF ENVIRONMENTAL HEALTH SCIENCES

053
N3695
1967/68

NATIONAL INSTITUTES OF HEALTH
NIH LIBRARY

AUG 5 2000

BLDG 10, 10 CENTER DR.
BETHESDA, MD 20892-1150

PUBLIC HEALTH SERVICE U.S. NATIONAL INSTITUTES OF HEALTH,
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY,
Report of Program Activities
July 1, 1967, through June 30, 1968

<i
753
12695
967/68

ANNUAL REPORT

TABLE OF CONTENTS

Page

COMPUTATION AND DATA PROCESSING BRANCH

Summary----1
Objectives----1
Current Programs----2
Program Progress and Accomplishments----3
Publications----6

LABORATORY OF APPLIED STUDIES

Summary----9
Objectives----9
Current Projects----10

Research Projects Report

3.1 "Mathematical Problems of Sequence Determination of Nucleic Acids and Proteins"----14

3.2 "Graph-Theoretic Analysis of Polymer Sequencing Data Obtained by Fragmentation"----16

3.4 "Statistical Research in Clinical Pathology"----18

3.5 "Heart Surgical Suite Project"----20

3.6 "Computer Modeling of Arrhythmias"----22

3.7 "Application of Advanced Mathematical Techniques in Surgical Neurology"----24

3.9 "Time Series Analysis Package"----26

3.10 "Biological Model Evaluator Studies"----29

3.11 "Computer Simulation Methods and Related Statistical Methodology"----32

3.12 "EKG Modeling and Analysis"----34

3.13 "The Statistical Analysis of Percentage or Proportional Data"----36

3.14 "A Range Distribution and Related Tests for Homogeneity"----38

3.15 "Interview Scheduling for Clinical, Research and Staff Associate Applicants"----39

3.16 "Signal-Noise Relationship in Neuroelectric Data"--41

COMPUTER SYSTEMS LABORATORY

Summary--43
Objectives--43
Program Progress--44

Research Project Reports

4.1 "Dental Institute Computing System"--49

4.3 "Study of Hybrid Computer Utilization in Support of Laboratory of Metabolism, NHI"--51

4.4 "Hospital Patient Record and Information and Retrieval System"--52

4.5 "Sequence Determination of Proteins and Nucleic Acids"--54

4.8 "Support of Programmed Console"--56

4.9 "Hybrid Computer Project"--58

4.10 "Computer System for Biochemical Laboratories of NIAMD"--61

4.11 "Computer Applications to Mass Spectrometer Data"--63

4.12 "Data Management Systems for the Myocardial Infarction Research Unit Program"--65

4.13 "Special Purpose Data Processing Systems for NHI and NCI"--67

4.14 "Combined Event and Time Code Generator and Reader Units"--69

4.15 "Beat-to-Beat ECG Analysis"--71

4.16 "Principles of Global Organization in Dense Volumetric Memories"--73

4.17 "Data Compaction"--75

4.18 "File Structure and Retrieval Processing System"----77

4.19 "Information Retrieval and Natural Language Data Processing"--79

Page

4.20 "Experimental Medical Telecommunications"------------82

4.21 "Analysis of Laboratory Spectral Data"---------------84

4.22 "Bone Mineral Mass Measurement in-vivo"--------------86

4.23 "Remote and Satellite Computation for National Institutes of Mental Health Building 10 Scientists"-88

4.24 "Gerontology Research Center Computing System"-------90

4.25 "Computer System for the Laboratory of Psychology, Section on Comparative Behavior, Poolesville"-------92

PHYSICAL SCIENCES LABORATORY

Summary--94
Objectives---94
Progress of Current Programs-------------------------------94
Program Plans--96

Research Project Reports

5.1 "Theory of the Ultracentrifuge"----------------------98

5.2 "Theory of the Helix-Coil Transformation in Polypeptides in Solution"-------------------------100

5.3 "Computer Processing of Nuclear Magnetic Resonance (NMR) Spectral Data"--------------------102

5.4 "Molecular Model Building Using Theoretically and Empirically Determined Intra-and Intermolecular Potential Functions"----------------104

5.5 "Biophysical Analysis"------------------------------106

5.6 "Physico-chemical Properties of Macrocyclic Antibiotics"--108

5.7 "Excitation and Transport Properties of Fluids"-----110

5.8 "Intermolecular Forces Acting in the Cell Membrane"---112

5.9 "Consulting Services"-------------------------------114

5.10 "Fundamental Studies"------------------------------116

Page

HEURISTICS LABORATORY
Summary---120
Objectives--120
Progress--120
Research Project Reports
6.1 "Automatic Question-Answering"------------------------123

6.2 "Biological Image Processing"-------------------------125

July 1, 1967, through June 30, 1968

PUBLIC HEALTH SERVICE-NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT-2
Serial Number

2. COMPUTATION AND DATA PROCESSING BRANCH

3. H. J. Juenemann
Acting Branch Chief

I. SUMMARY

During Fiscal Year 1968, the conversion effort which, in the previous year, had consumed almost all CDPB resources and efforts was continued, but more significantly it was finally completed. All of NIH's central computing responsibilities have now been converted to the multi-machine IBM 360 configuration. Both Honeywell 800 Computers have been released. In addition, significant advancements were made in modifying the vendor-supplied operating system to provide reliable, efficient and responsive machine servicing to the wide variety of NIH computer needs. A significant start was made toward providing an NIH based system of remote stations accessing to the central computers. Computational and programming support to NIH research and management programs was increased. By virtue of the completion of the conversion effort and by virtue of improved systems performance, the Branch was able to tailor more specific and responsive support to broad categories of NIH computational needs. The mode of advice and assistance to help the NIH user assume greater responsibility for guiding his own computational efforts was successfully emphasized.

Recognizing ever-increasing involvement of computing in NIH's daily life and recognizing maturation of computing into the broader world of NIH's research philosophies, the discontinuation of CDPB as a separate organization focused on revolving fund operations was proposed and (hopefully) approved. This annual report is then the final one for CDPB as an organizational entity spanning the formative years of computing in biomedical research. From Fiscal Year 1954 through 1968, CDPB gave birth to the sometimes faltering computing capabilities of NIH by first placing computers into the service of NIH research and its management. The development of DCRT's capability for fully integrating computing and computational sciences into the every day life of NIH research and its management is both a reason for and, in fact, a fitting epitaph to the organizational entity known as CDPB.

II. BRANCH PROGRAMS

A. Objectives

The Computation and Data Processing Branch provides a central facility for professional programming, computing and data processing services for NIH. It maintains operational liaison with research investigators, program officials and administrators in the effective use of its computational and data processing services. The Branch performs all phases of centralized computation and data processing, using general purpose digital computers, data conversion equipment, other peripheral equipment and EAM equipment. Develops general purpose, user-oriented computer systems, routines and subroutines; coordinates the use of Branch equipment in both central and peripheral locations; and exchanges technical knowledge and operating experience with other organizations engaged in computation and data processing in support of biomedical research and related activities.

B. Current Programs

During the first quarter of the year, major efforts continued to be absorbed by the dual task of conversion to new equipment and that of modification of vendor supplied software to adopt it to the NIH environment and to convert it into a responsive and reliable system. The majority of the conversion effort was completed at the end of the first quarter of the year and the first of the two Honeywell 800 Computers was released in September, 1967. The few remaining programs were soon converted to the 360 and the second H-800 was released in April, 1968. The contractor who had been involved in the conversion was released. The H-200, which had originally been procured as an input-output adjunct to the two H-800's, continued its role as a media conversion device (paper tape to magnetic tape, reformatting 2nd generation tapes to those required by the 360's, etc.), but in addition, its modest power (and, therefore, modest cost) was increasingly applied to input editing and data preparation tasks formerly performed on EAM equipment.

The second of the Branches' major endeavors for the year, largely successful at year end, has been to mold the vendor-supplied 360 software into the reliable, responsive and expandable system required by the fantastic variety of demands placed on central computer facilities of NIH. The vendor-supplied software system, called Operating System 360, which controls the processing of jobs through the computers, was at the beginning of the year far from adequate to NIH's needs and, in fact, was far below what the supplier had promised. One significant factor which was also typical of a general situation, was that each individual job tied up the whole machine configuration, even when it was only reading input or printing output. These types of limitations, falling short of promises, combined with continued hardware maintenance and delivery problems had lead the Appropriations Committees of both Houses of the Congress to note in their report on the Fiscal Year 1968 appropriations hearings the critical situation existing at NIH. As a result of our own constant pressure, aided by the Congressional Reports, a major joint effort was mounted between NIH and the vendor. One of the first fruits of this was a significant improvement in hardware reliability and elimination of a large backlog of pending hardware modifications. As a second major result, operating system components were supplied to NIH and modified to suit NIH's systems. These allowed the computers to operate with four simultaneous "streams". While computation of one program is under way, input for the next few jobs is simultaneously being read in and stored. Results for the last several jobs are also simultaneously being printed, with one output "stream" and one printer devoted to systems messages, diagnostics and small scientific results which have immediate relevance and another output "stream" and printer devoted to those very large printing loads which result from administrative and management data processing. A third significant advancement was that, in spite of the vendor's initial doubts, NIH succeeded in developing the software modifications to enable one disk storage unit to be simultaneously shared and accessed by two different computers. This eliminated the need to store program and procedure libraries redundantly on each machine. Developmental efforts are underway to extend this capability to three or more machines and to include data as well as programs and procedures. A fourth area of intensive software improvement effort was the implementation of geographically remote stations for input and output of computer runs. By year-end two small computers had been attached to the larger computers via telephone lines and it was shown that a wide range of computing jobs could be effectively submitted to the central computers from remote sites. Software developmental efforts are also underway to introduce conversational type computing from remote sites and to use several forms of graphic displays for text output.

C. Program Progress and Accomplishments

1. Analysis and Programming

The Branch function to provide computer programming capabilities in support of NIH research and management functions was able to be accelerated during the year due to the completion of the hardware conversion effort. In the face of ever-growing demands, the effort to transition the programming functions from a role of "service" to one of "advice, assistance and the development of computational tools" was accelerated. The advice and assistance role is a necessary and implicit adjunct to the tool library development role because no tool is useful unless supplemented by technically competent personnel available to inform potential users of its availability, advice on its applicability, assist in its use and most importantly to maintain, modify and expand its capabilities. The following are examples of this new image.

a. Tablemaker II is the Branch's most successful tool development accomplishment. Early in the year Tablemaker II became operational on the new hardware. The system had resulted from a reworking, expansion and improvement of an earlier CDPB-developed Tablemaker I. This tool typically allows a bio-statistician, a program analyst or similar professionals, who have no experience with computers, to take a basic file of data, extract relevant information, recode the control variables or otherwise regroup or re-express the data. The data can be operated on by logical or arithmetic operations to compute frequencies, averages, expectancy tables and then presented along with appropriate descriptive material in tabular form. Heavy use of this tool is made at NIH where a significant portion of the research involves the deductive analysis of bodies of observed data. While it was a significant accomplishment to provide this tool, it was perhaps more significant that the system can, and is now, heavily and easily used directly by investigators with the central programming staff providing only consultive assistance.

b. During the year a query package was also adopted and expanded from the earlier CDPB developmental effort. The query system provides an easy to use tool for "browsing" and recalling data from any pre-existing data file based on complex logical statements of conditions. One significant aspect of the new version of the query over its predecessors is it can be used with any of a wide variety of file structures including those where the file structure is itself variable.

c. The development of a DCRT Program Library for the 360's came to realization during the year. A Booklet describing over 300 programs available in our program library was prepared and distributed. The major effort has first been concentrated in the areas of statistics and mathematics. Concurrently, work is also going on in the areas of Information Display, Data Processing Procedures and Special Languages. Significantly, all of these programs have been tested, documented and are accompanied by user oriented instructions to make them an attractive and easy to use substitute for reptetive programming each time the same computational situation is encountered.

d. At year end, multiple efforts are underway to build data file creation, editing and updating tools which will operate either in the normal batch processing central facility mode or can be used via remote access points. These file creation and data editing tools will, when viewed in conjunction with the computational library, the query, tablemaker and other standard programs, allow a complete task to be handled using a variety of tools appropriate to each part of the process.

2. Computer Operations

Throughout the fiscal year, the Branch operated two 360/50's and a 360/40. The former were dedicated to the general computational requirements of NIH research and management while the latter was used almost exclusively in support of the administration of NIH's extramural programs. In May a third 360/50 was added as was the capability for two of the 360/50's to share common libraries. The number of productive hours during which these computers are being applied to computational tasks continued to grow. During the 3rd quarter of the fiscal year the average was 425 hours per machine of production time. More indicative of the general improvement are the figures on turnaround time (the elapsed time between the time a programmer submits his job and the time he received results) and secondly, the total number of jobs processed per day. For the daylight shift, when the predominant use of the computer is for testing new programs, the turnaround time was reduced to a 3rd quarter average of 1 and 3/4 hours. During the night shifts, when the primary use of the computer is for large or "production" runs, the average 60 hour turnaround during the first quarter of the year had, by the third quarter, been reduced below 16 so that in almost all cases all work submitted one day is completed by the next morning. At the same time the number of runs processed daily has increased from 80 to over 450 per day.

3. Computer Training for Scientists

In order to foster the concept of having NIH investigators take added responsibility for programming their own computation relying only on advice, assistance and tools being provided centrally, the training unit of the Branch provided programming training for 155 scientists. The number of scientists doing their own programming rose from last years mid-year figure of 127 to a third quarter figure for this year of 241. During the year the training unit has added to its curriculum instruction in the use of commercially available remote computing services and the Job Control Language of the 360 Operating System. A course in the PL-1 programming language was, at year end, being developed to augment the training in Fortran.

4. Machine Tabulation

During the year the Machine Tabulation function added the Honeywell 200 computer to its Electrical Accounting Machine (EAM), "punched card" and data preparation operations.

a. The Keypunching operations of the Branch continued to operate beyond its capacity throughout Fiscal Year 1968. This, coupled with a shortage of personnel, forced delays in service and necessitated occasional use of outside contracts. Approximately 300,000 cards are punched each month by Branch personnel and approximately 18,000 per month by contractors. It is significant to note that the cost has been consistently lower for inhouse keypunching as compared to contract keypunching. This cost benefit is maintained in spite of the fact that only the more simple high volume jobs can be done on contract.

b. The EAM Unit, located at the Westwood Building, continues to provide specifically tailored punched card service to the Extramural Program Management Offices located in the Westwood Building. This Unit, throughout the year, maintained an outstanding level of service by consistently meeting tight deadlines in spite of continuous personnel shortages. The Westwood operation also includes a do-it-yourself facility for the exclusive use of certain Grants Management Operations. Utilization of this Unit increased constantly during the year as more and more program managers availed themselves of the almost instantaneous assistance available even from relatively unsophisticated equipment. At year end some of the applications currently being processed on Westwood EAM equipment is being evaluated for conversion to the IBM 360 or the H-200.

c. The on-campus EAM Unit at the Central Facility continued during Fiscal Year 1968 to complete their reorientation. Large on-going 360 computer systems which previously also involved EAM processing steps which are gradually being redesignated to reduce the EAM processing operations to those associated with input data preparation and validation and this form of processing is being redirected to the H-200. Another major segment of the work of the EAM Unit is that which for economic reasons is best processed on small inexpensive equipment. A significant portion of this load has been reoriented to partial or complete H-200 processing by making use of COBOL and a few standard EAM simulator type programs.

5. Field Activities

The Branch continued its support of the NIAID project at the Middle Atlantic Research Unit in Panama. The CDPB staff member there had, in the previous fiscal year, established a punched card (EAM) system which succeeded in gaining control over the large amounts of basic data needed to support the virological research at MARU. During this fiscal year attention was gradually diverted to data analysis and significant use of the computer facilities of a neighboring Federally supported installation.

During the year the Branch provided extensive analysis and programming support to the Clinical Field Studies Unit, NIAMD, located in Phoenix, Arizona.

6. Publications

Gordon, M. H.: DCRT Program Library Booklet, June 1968.
Krichevsky, M. I., Zaveler, S. A. and Bulkeley, J.: Computer-Aided Single or Dual Isotope Channels Ratio Quench Correction in Liquid Scintillation Counting. Analytical Biochemistry, Vol. 22, #3, pp. 442-464, March 1968.

Podolsky, R. J., Shapiro, N. Z. and Zaveler, S. A.: Isotonic Velocity Transients in Models of Muscle Contraction. Federation Proceedings, Vol. 26 #2, Abstract #1659, pp. 553, March-April 1967.

Maloney, C. J., Bryan, S. and Epstein, M.: Computer assisted primary index preparation. J. Chem. Documen. 7, pp. 223-232, November 1967.

7. Administration

As noted in the summary, this fiscal year was the last for the organizational entity of the Computation and Data Processing Branch. The Branch had begun in 1954 as a marriage between some punched card equipment used by the accounting staff and a unit headed by the noted epidemiologist, Dr. Harold Dorn. The Branch continued to rely on EAM equipment until 1958 when the first computer was installed. This was installed almost as an act of faith in the belief that there was a potentially valuable role which computers might play in biomedical research. This potential was slow to develop and that computer, an IBM 650, was used primarily for administrative work. Only a few pioneering investigators dared. Parenthetically, one of these pioneers was to become, in 1966, the Director of the Division of Computer Research and Technology.

The lack of scientific use of the 650 was only partly due to reluctance. It was also due to the nature of that machine. In December of 1960, a Honeywell 800 was installed. It experienced hardware and software troubles, quite similar to the troubles to be experienced in 1966 when the current equipment was installed. However, by late 1961, these troubles had been largely overcome and the scientific use of the H-800 began to increase more rapidly than its administration use. In May of 1963, the growing workload required installation of a second H-800. Recognizing the growth rate for what it was, the start of a new era, a series of studies were undertaken to examine the future needs of NIH. These studies were completed in 1965 and IBM series 360 equipment was selected. A long and sometimes torturous conversion effort was started with the first 360 equipment installed at NIH in April 1966 alongside the two Honeywell H-800's and the H-200 which had been added in 1964. In this fiscal year--in April 1968--the end of the conversion effort was marked by release of the second of the two Honeywell 800's. The conversion from second generation medium scale Honeywell equipment to large scale so-called third generation IBM series 360 equipment thus spanned the period from June 1965 to April 1968. The problems and difficulties with hardware deliveries, hardware performance, software deliveries, software performance, the operating system, the programming contractor, changing and growing NIH workloads during a protracted period of overlap and conversion and many other problems are well known. Now that they are past, they can in retrospect be viewed as having helped to mature the Division.

The history of CDPB's hardware oriented development is paralleled by developments in the analysis and programming components. The current major emphasis on the concept of developing tools which are applicable to a general class of problems has a thread dating back to 1962. Because many NIH scientific computations involve large amounts of data, we enriched the vendor supplied Fortran compiler with a package of about 20 subroutines which provided the scientifically oriented Fortran language with some appropriate data manipulation capability. This package has been continuously used and during this year became operational on the new hardware. In 1964, the Branch developed a query program which although, in its first version, was specific to the NIH Extramural Core Data File, was the progenerator of the improved version completed this year. The Tablemaker system first became operational in 1964 and was soon followed by a generalized file merging tool. The first library of scientific programs was made available in 1964 containing roughly 100 programs, many of which were not fully tested. This compares with more than 300 in the current DCRT Program Library.

Other indicators of the growth of computing at NIH are the fact that in Fiscal Year 1962, the Branch had 103 persons on its staff and a gross value of $1,470,000.00 for the reimbursement of the costs of the services it rendered. In June of 1967, there were 201 persons on duty with the Branch who rendered services valued at $3,800,000.00.

The foundation of DCRT in June of 1966 was prompted in part of share growth in the amount of both scientific computation and management data processing at NIH. It was equally, however, the result of the gradual realization starting perhaps with various committees and studies made since 1963, that the relationship between computing and biomedical research and its management is much more than a relationship of service. Because of this, the accumulated experiences and resources of CDPB were part of the nucleus for the new Labs and Branches of DCRT. Rather than merely saying that the organization known as CDPB ceased to exist in Fiscal Year 1968, it is more accurate to say that CDPB was absorbed into all phases of the larger concept which is DCRT.

July 1, 1967 through June 30, 1968

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Laboratory Activities	1. DCRT-3 Serial Number
2. LABORATORY OF APPLIED STUDIES	3. Eugene K. Harris, Ph.D. Chief

I. GENERAL SUMMARY

The primary function of this Laboratory lies in the application of mathematical statistics, mathematics and computer technology to areas of laboratory and clinical research at NIH where opportunities exist and the need is clear for productive collaboration between biomedical and mathematical or computer scientists. In the Laboratory's first Annual Report (FY 1967), a number of collaborative projects were identified, particularly in cardiology, neurology, metabolic studies, and clinical chemistry. Planned objectives of almost all of these research projects described in last year's report have been reached. In support of these projects, and for general use at NIH, two large computer programming systems have been completed, one concerned with the management of continuous pressure and flow data obtained during heart surgery and in catheterization laboratories; the other, a comprehensive set of linked programs for time series analysis. Further, the Laboratory has completed independently-generated research in non-parametric statistical methods and has developed specialized computer programs for multivariate analysis, particularly useful at NIH. Considerable progress has also been made on a promising mathematical approach to the determination of molecular structures from fragmentation data after enzymatic digestion.

II. CURRENT LABORATORY PROGRAMS

A. Objectives

1. To initiate or join in sound collaborative research involving the application of mathematical statistical theory and related computer technology to problems of importance in experimental and clinical medicine.

2. To research and test new mathematical statistical methodology or mathematical models useful in the study of physiological and general biological processes of medical significance.

3. To support these research efforts through the development of specialized computer programs to test biomathematical models and facilitate the analysis of laboratory and clinical data, often collected continuously in analog form and requiring analog-digital conversion.

B. Summary of Current Projects

1. Collaborative Studies with Surgery Branch, NHI, and Surgical Neurology, NINDB.

Research studies pursued during this past year have followed upon the perfection of three fundamental tools required for substantive applications of computer science and mathematical methods in these areas. These tools included two large programming systems begun during last Fiscal Year, extended, fully documented and catalogued for routine use on the computer during this Fiscal Year (DCRT Project Nos. 3.5 and 3.9). The first of these was a system of linked computer programs to analyze continuously recorded measurements of ventricular and aortic pressures, aortic flow and the corresponding EKG. This has been supplemented by an extensive array of automated graphic outputs. Recent experimental use of these programs has included (a) measurement of valvular efficiencies by determining energy losses across normal valves and in valves of patients suffering from idiopathic hypertrophic subaortic stenosis; (b) testing and improving current methods for assessing aortic orifice area by detailed examination of dynamic changes affecting orifice area during a single cardiac cycle; (c) calculation of reverse flow in the aorta which may lead to a better measurement of coronary blood flow.

In addition to the cardiac computer programs, these research studies have depended on the use of precise, compact analog recording and editing equipment, specified and installed by this Laboratory during the early part of this Fiscal Year, and now used routinely in both cardiologic and neurologic research studies. This equipment and the computer programs applied to the recorded data, now enable the investigator to undertake on an efficient basis detailed beat-by-beat analyses and comparisons of the dynamic events occurring during heart contraction. For example, in another of the Laboratory's research studies in cardiology (DCRT 3.6), initiated during the previous reporting period, cross-correlation between EKG patterns of consecutive beats in arrhythmias has proven to be a rapid technique for the diagnosis of different kinds of arrhythmias which may provide considerably more discriminating power than current methods based on changes in beat-to-beat intervals alone. Although written in FORTRAN, these correlation programs run in less than real-time (i.e., less than the time required to collect the data on analog tape). Plans are currently under way in cooperation with the Computer Systems Laboratory, DCRT, to incorporate this technique in specially designed, compact hardware for use in the intensive care of cardiac patients.

Studies of electroencephalographic changes in split-brain chimpanzee preparations begun during FY 67 (DCRT 3.7) have been accelerated during the past year through the use of the (portable) recording equipment mentioned above and also the completion, cataloging and documentation of the set of computer programs for time series analysis

(DCRT 3.9) mentioned earlier. In this collaborative study with Surgical Neurology, power spectral analysis was used to study electroencephalographic changes following unilateral section of the brain stem in split-brain chimpanzees. Although gross neurological and social performance did not appear affected, mathematical analysis showed marked changes in distribution of slow and fast frequencies after brain stem section which may reflect differences between the hemispheres in motor dominance. These studies of EEG records in chimpanzees are continuing; in addition, a recent collaborative study undertaken with Surgical Neurology [NINDB NDB(I)-62 SN/OC 913(c)] has involved the collection and analysis of single- and multiple-cell recordings simultaneously from both right and left motor cortexes in animals and in patients with Parkinson's Disease. These studies hope to define more closely the transmission of information following stimulus at lower levels in the central nervous system. Substantial use of the hybrid computing equipment and statistical programs for the analysis of series of events are required.

2. Mathematical Modeling and Statistical Research

During the past year, much more extensive use has been made of the Biological Model Evaluator, a programming system for the development and testing of mathematical models descriptive of physiological processes (DCRT 3.10). Studies in calcium and sodium kinetics have been continued and new projects undertaken this Fiscal Year concerning the transport and utilization of free fatty acids.

One of the important functions of mathematical statistics within this Laboratory in support of computation generally and statistical research in particular, is the development of specialized programs to handle advanced statistical methodology. In recent years, one of the most useful products of this effort has been the random number generator now available for routine use on the IBM 360 system. Building on this technique, a procedure has been developed for generating random samples from normal multivariate populations (DCRT 3.11). In addition, under the guidance of the Statistics and Quantitative Biology Section of the Laboratory, useful programs for discriminant function analysis, including a nonparametric procedure, have been prepared.

One example of an application of mathematical theory (in this case, the algebra of determinants) to solve a management problem at NIH has been the development of an algorithm and corresponding computer program to automate the scheduling of interviews for research, clinical and staff associateships at NIH (DCRT 3.15). Programming and testing were completed in the fall of 1967 and the system fully implemented in January, 1968, for regular operation, during May, 1968, in place of the manual system heretofore used for interview scheduling. It is anticipated that use of the automated system will provide the NIH scientific and clinical staff a valuable 2-3 week additional time period for reviewing applications of associateship candidates.

More fundamental statistical research aimed at increasing the store of advanced statistical methods available to the NIH scientist concerns the analysis of proportions (a continuing and now completed project, DCRT 3.13) and a nonparametric test for the homogeneity of ranges of discrete variables (DCRT 3.14).

In a continuation of previous work on the mathematical determination of molecular structure from fragments obtained after enzymatic digestion (DCRT 3.1) work has been completed on the proof of necessary and sufficient conditions for unequivocal solution of a nucleic acid sequence. A new, supplementary project (DCRT 3.2) in this area concerns an intensive study of graph-theoretic methods, which may lend themselves to the design of relatively simple, efficient algorithms for computer or manual evaluation of fragmentation data.

3. Related Collaborative Studies in Applications of Statistical Methodology

a. Clinical chemistry (DCRT 3.4)

Considerable progress has been made in continuing statistical analysis to determine components of variance in determinations of serum constituents among normal individuals and patients. Analysis of 15 serum variables in 78 normal volunteers is now essentially complete and a series of reports is being prepared on sample selection, laboratory procedures, statistical analyses, and clinical significance of findings, in cooperation with the Clinical Pathology Department of the Clinical Center. When this landmark information is published, it will make available for the first time a well-founded basis for assessing the variability found in multi-phasic screening programs which typically obtain only single samples from each individual. Surprising results have been obtained, for example, regarding the ratios of intra- or inter-individual variation to analytical error, indicating that in some variables, the body exercises a tight physiological control as yet unmatched by the best clinical tests.

b. Signal/"noise" relationships in bioelectric activity (DCRT 3.16)

This project, discussed in the last Annual Report, has succeeded in achieving the goals set for this year. A 360-program for adaptive filtering of signals in band-limited noise has been completed and documented. Supplementing this program are new, efficient programming methods for band-limited noise generation which make use of the random number generator mentioned earlier. These programs have been used to validate a method, conceived last year, for estimating unknown signal/noise levels in prefiltered sample records. Artificial, time-locked sine waves and exponential signals over a 25-fold range of signal/noise level, imbedded in noise of various bandwidths have been subjected to adaptive filtering. Based on statistical analysis of the filtered output, a procedure for characterizing noise patterns in relation to signal content, and for estimating signal/noise ratios has been proven essentially independent of waveform and therefore of wide application to the analysis of bioelectric signals. For example, it should prove particularly useful for characterizing changes in the organization of background neural activity during the course of habituation to stimuli.

C. Other Activities: Organizational Developments

Laboratory staff members served on the faculty of the Foundation for Advanced Education in the Sciences, teaching two courses: (1) Elementary Probability for the Biological Sciences, and (2) Time Series Analysis.

The most significant change in organization affecting this Laboratory during this reporting period was the recent transfer of the mathematical, mathematical and statistical and library programming units from the Computation and Data Processing Branch to the supervision of this Laboratory.

Note: One research project identified with this Laboratory in last year's Annual Report (DCRT 3.14: Molecular Model Building using Theoretically and Empirically Determined Intra- and Inter-Molecular Potential Functions) has been transferred to the Physical Sciences Laboratory (DCRT 5.4). Another project (DCRT 3.8: A Mathematical Model to Study Cerebral Concussion and Related Brain Trauma) has been incorporated in Project DCRT 3.7: Application of Advanced Mathematical Techniques in Surgical Neurology.

Serial No. 3.1
1. Lab. of Applied Studies
2. Stat. & Quan. Biol. Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Mathematical Problems of Sequence Determination of Nucleic Acids and Proteins

Previous Serial Number: Same

Principal Investigator: James E. Mosimann, Ph.D.

Other Investigator: Jay Vinton

Cooperating Units: Computer Systems Laboratory, DCRT

Man Years (computed for the 12 month period):

Total:	0.2
Professional:	0.2
Other:	0.0

Project Description:

Objectives:

1. To provide mathematical definitions of classes of protein and nucleic acid sequences which cannot be determined using complete digest methods.

2. To provide a probability framework for evaluating the probability that protein and nucleic acid sequences of certain classes are solvable, using partial digest methods.

3. To provide mathematical support necessary for testing computer programs designed to reconstruct nucleic acid and protein sequences from fragment data.

Methods Employed:

The primary mathematical tools are (1) algebra, specifically, the algebra of free monoids; (2) graph theory; and (3) stochastic processes, Markov chains.

Major Findings:

Necessary and sufficient conditions have been obtained for sequences to be solvable using complete digestion fragments. There are broad classes of sequences which cannot be determined by complete digests with monobase specific enzymes. The theoretical studies clearly indicate the need for partial digest fragment data in determining sequences of nucleic acids.

Significance to Biomedical Research:

Determination of the primary structure of proteins and nucleic acids is of extreme importance in studies of the genetic code, as well as molecular bases of life.

Honors and Awards: None

Publications:

Cahiers d' etudes biologiques, Universite Catholique de Lyon, Lyon, France. In press.

Serial No. 3.2
1. Lab. of Applied Studies
2. Biomedical Studies Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Graph-Theoretic Analysis of Polymer Sequencing Data Obtained by Fragmentation

Previous Serial Number: None

Principal Investigator: George Hutchinson, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years (computed for the 12 month period):

Total:	0.6
Professional:	0.6
Other:	0.0

Project Description:

Objectives:

To create a mathematical model of experiments in molecular biology which determine protein and nucleic acid sequences by fragmenting the polymer through complete or partial digestion, and determining the fragment sequences.

To develop mathematical criteria by which inconsistencies in experimental data can be detected, by which a polymer sequence or sequences consistent with the data can be computed, and by which all alternative possibilities can be eliminated.

Methods Employed:

Fragment sequences from an unknown protein or nucleic acid sequence are presumed given. A mathematical model using a modification of the theory of graphs (i.e., networks) was developed. A special graph is constructed from any given data configuration of a certain class. Inconsistencies of the data are revealed during the construction process or by simple tests on the constructed graph.

The polymer sequences consistent with the given data are in one-one correspondence with the Euler circuits of the constructed graph. If an Euler circuit is known, the corresponding polymer sequence can be recovered immediately. Therefore, the constructed graph holds the complete solution of the problem in a compact form.

A method of generating all of the Euler circuits of any such graph has been developed. Euler circuits are efficiently generated one by one, and the process can be cut off if the number becomes too large. So, it is possible to efficiently recover all polymer sequences yielding the given data, unless there are too many.

Major Findings:

The graph-theoretic model has been developed for the common situation in which complete digests by pancreatic ribonuclease and by T_1 ribonuclease are available. Complete analysis of data of this type can be made. Criteria have been developed to determine whether the data are inconsistent, to determine the polymer sequence of sequences consistent with the data, and to eliminate all alternative possibilities. Efficient algorithms are available for these computations. The present results are primarily useful in detection of inconsistencies, since two complete digests do not usually provide enough data to uniquely determine a polymer sequence.

Significance to Biomedical Research and the Program of the Institute:

Successful development of this approach would aid researchers in molecular biology to quickly and accurately evaluate experimental data, to detect erroneous data, and to avoid redundant laboratory effort.

Proposed Course of Study:

To extend the graph-theoretic model to accommodate more general configurations of complete and partial digest data.

To design and prepare a computer program or programs for evaluation of polymer fragment data by the graph-theoretic method.

Honors and Awards: None

Publications: None

Serial No. 3.4
1. Lab. of Applied Studies
2. Office of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Statistical Research in Clinical Pathology

Previous Serial Number: Same

Principal Investigator: Eugene K. Harris, Ph.D.

Co-Investigators: Ernest Cotlove, M.D., Clinical Pathology Dept., CC
Donald Young, M.D., Clinical Pathology Dept., CC
George Shakarji, LAS, DCRT

Man Years (computed for the 12 month period):

Total:	.85
Professional:	.75
Other:	.10

Project Description:

Objectives:

To explore, through careful application of statistical methodology, relationships inherent in large volumes of results of chemical analyses routinely performed on serial blood samples from normal volunteers and patients at the Clinical Center.

Methods Employed:

At this time, blood chemistries from 78 normal volunteers, in ten groups of seven or eight individuals per group, are stored in easily retrievable form on digital magnetic tape. These data consist of concentrations of at least 15 elements and compounds (including some enzymes) measured in each of 10-12 weekly blood samples from each subject. The total ten-group data base covers a 2 1/2 year period of study, and includes approximately 26,000 measurements.

Similarly stored patient blood data are available from approximately 2500 Clinical Center admissions during a 9-month period in 1964-65. Demographic and diagnostic information on these patients is also available for related study. Serial blood data for each patient is less abundant than for normal volunteers and not regularly spaced, but does permit some time-wise analyses relative to effects of therapy or other changes of state.

A separate component of variance analysis has been applied by computer program to the weekly concentrations for each normal volunteer. The availability of daily measurements on pooled frozen serum allowed separate estimation of analytical error, so that weekly variation in a subject's results can be apportioned to (a) inherent physiological variability, (b) fluctuations in routine laboratory analysis of replicate samples. Analysis of variance of the subject means permitted estimation of inter-individual variance components.

Major Findings:

During the past year, variance component analysis in the normal control data has been completed, as have many auxiliary analyses testing age-race-sex differences, as well as factors related to laboratory quality control, and to the validity of various statistical estimates. A series of reports concerning sample selection, laboratory procedures, results of statistical analysis and their significance for clinical medicine are now in the final stages of preparation.

Significance to Biomedical Research:

These studies will (1) add substantially to existing information on physiological variation of blood constituents within a single healthy individual over time and among normal individuals within a given age, sex, and race group, and (2) provide new knowledge on currently achievable analytical precision (e.g., in the course of multiphasic screening programs), and (3) provide an opportunity to test potentially useful mathematical models of time-dependent changes in blood constituents of patients during the course of therapy.

Proposed Course of Project:

Further analysis of data from normal subjects will study possible inter-relationships among different blood constituents. One specific aim will be the development of a function of several variables which may provide a distinctive blood "profile" of a normal individual. Later, attention will be centered on the patient file, using distributions of blood tests in normal volunteers to aid in isolating extreme ranges in each variable among patients. Correlations among extremes and relationships to diagnosis and to demographic variables will be examined, and relevant physiological hypotheses will be tested. Finally, the variation in each test over time will be studied in relation to early and final diagnoses and course of therapy. At this point, more sophisticated mathematical statistical methods, drawn from the theory of stochastic processes, will be needed to describe dynamic changes in test results during hospitalization.

Honors and Awards: None

Publications: None

Serial No. 3.5
1. Lab. of Applied Studies
2. Biomedical Studies Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Heart Surgical Suite Project

Previous Serial Number: Same

Principal Investigator: David B. Gilbert, M.D.

Other Investigators: Thomas F. Lantry, LAS, DCRT
Martha R. Horton, LAS, DCRT

Cooperating Units: Dr. Andrew G. Morrow, Surgery Branch, NHI
Dr. Stanton Nolan, Surgery Branch, NHI

Man Years (computed for the 12 month period):

Total:	1.7
Professional:	1.7
Other:	0.0

Project Description:

Objectives:

The goals of the Heart Surgical Suite Project are to provide accurate, well-organized mathematical analyses of massive quantities of physiological data obtained from humans during surgery.

Methods Employed:

Data acquired in analog form on magnetic tape during surgery are edited off-line on equipment designed by the Division. The data are then converted to digital form on the CDC 3100. The digital tape is analyzed off-line on the IBM 360 system utilizing FORTRAN and assembly language programs. The parameters presently include two pressures, the flow between these two pressures, and the electrocardiogram. Classical analyses of this data include the maxima and minima of flow and pressure, rates of flow and pressure change, stroke volume, stroke work and power. Experimental analysis includes the energy loss across a diseased valve expressed as valvular efficiency and the distribution of the fractional energy loss throughout a cycle. Reverse flow in the aorta is also calculated.

Major Findings:

The FORTRAN programs for off-line analysis of pressure-flow characteristics were completed and checked out. The data acquisition and display hardware was completed and operational; they were used almost daily not only for the DCRT-NHI project but for DCRT-NINDB projects as well.

Utilizing the hardware and software developed, the non-steady-state characteristics of post premature contractions in idiopathic hypertrophic subaortic stenosis has been documented and quantitated. The nonlinear relationship between empirical indices (gradients valve areas, tension-time indices) and the actual disturbed flow energy losses have been described.

Using selected portions of the developed software, the relative efficiences of mitral ball and disk valves have been studies in the calf. Optimum cardiac outputs for minimal frictional energy losses were defined.

Significance to Biomedical Research:

The development of a hardware and software package for the beat-to-beat analysis of pressure-flow relationships on a digital computer system has been completed. The mathematical, engineering and programming have been documented in detail and is available for other investigators.

Proposed Course of Project:

The completed software and hardware package is now available for NHI-DCRT collaborative projects. The programs are most suitable for describing non-steady-state phenomena in both the animal laboratory and the surgical suite environment. Various models of obstructed flow will be tested and analyzed with the programs; they will be compared to the results observed in vivo. A great bulk of the programs await implementation in the cardiac catheterization laboratory.

Honors and Awards: None

Publications: None

Serial No. 3.6
1. Lab. of Applied Studies
2. Biomedical Studies Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Computer Modeling of Arrhythmias

Previous Serial Number: Same

Principal Investigators: David B. Gilbert, M.D.
Eugene K. Harris, Ph.D.

Other Investigators: None

Cooperating Units: Surgery Branch, NHI (to supply data in the form of magnetic tapes)

Man Years (computed for the 12 month period):

Total:	0.0
Professional:	0.0
Other:	0.0

Project Description:

Objectives:

The immediate goal of this project is to simulate the sequential changes expected in cardiac conduction during rapid stimulation using the digital computer. Ultimately, the simulation of sequential electrical activity should aid in pattern recognition studies for classification of arrhythmias.

Methods Employed:

Utilizing known facts about transmembrane potential and thresholds of response for each of the pathways of cardiac conduction, a digital computer simulation of cardiac conduction has been programmed. The response of each nerve fiber is determined by its previous response and the input impulse. For a given number of cardiac cycles, the model will stimulate and plot the action potential of the sinoatrial node pacemaker, and atrial fiber conducting an impulse to the atrioventricular node and the effect of the A-V node upon a ventricular fiber.

Major Findings:

Due to pressure of other work, this project was suspended during FY 68, but will be resumed during the coming year.

Significance to Biomedical Research:

A general need is recognized for the adequate training of physicians to interpret cardiac arrhythmias. The proposed model graphically depicts each step of cardiac conduction as well as the expected time at which one would expect the atria or ventricle to fire. More specifically, the model should aid to our knowledge about the ventricular response to atrial fibrillation and how that response might be altered.

Proposed Course of Project:

The model is to be tested systematically for its ability to predict known changes recognized on the EKG. Data from individuals in known atrial fibrillation will be collected, and the resultant frequency distributions of the R-R interval will be compared to the digital computer simulation. The effects of respiration upon that distribution can be then studied from both a theoretical and experimental point of view.

Honors and Awards: None

Publications: None

Serial No. 3.7
1. Lab. of Applied Studies
2. Biomedical Studies Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Application of Advanced Mathematical Techniques in Surgical Neurology

Previous Serial Number: Same

Principal Investigator: Raymond Mejia

Co-Investigator: Dr. Maitland Baldwin

Other Investigator: Thomas F. Lantry, LAS, DCRT

Cooperating Units: Surgical Neurology Branch, NINDB
Technical Development Section, NINDB

Man Years (computed for the 12 month period):

Total: 1.0
Professional: 0.5
Other (including computer time): 0.5

Project Description:

Objectives:

The objective is to study physiological parameters available during surgery through the application of advanced digital processing techniques. Experiments using lower primates have been conducted, and studies are being carried out which include the mathematical analysis of patient data obtained in the Neurology recording facility.

Methods Employed:

LINC computer programs have been developed to accept analog data consisting of up to six physiologic variables and convert them to digital data in a form directly acceptable to the IBM 360 computer. Programs for the IBM 360 computer have been developed which quantify slowly changing variables (such as temperatures), continuously changing phenomena (such as EEG) and discrete variables (pulse rate, for example).

Major Findings:

In collaboration with Dr. Maitland Baldwin, Surgical Neurology, data was obtained and analyzed to study the effects of unilateral section of the brain stem after mesial cerebral incision[1] [NDB(I)-54 SN/OC 101(c)]. Chimpanzees subjected to mesial cerebral incision are capable of synergistic and other usual motor performance as well as normal social reactions despite severence of interhemispheral connections. Moreover, subsequent subtotal hemisection of the brain stem does not materially alter neurological or social performance nor is it followed by disturbance of nocturnal-diurnal cycles. However, both operations were followed by marked electroencephalographic changes. After mesial cerebral incision, there is an evident asymmetry while following brain stem section, the record is comparatively slower particularly on the side of section.

Significance to Biomedical Research and the Program of the Division:

In addition to the contribution to neurology and the art of surgery, the quantification of meaningful physiological parameters in a manner amenable to immediate as well as long term scientific study is significant. The development and application of suitable mathematical techniques of analysis is made possible in large part through the availability of adequate recording and computing equipment.

Proposed Course of Project:

A study of electroencephalographic changes due to subconcussive and concussive blows, which are measured on the cortex and in deep structures of the brain, is being conducted in collaboration with Drs. A. Ommaya and D. Gainsburg [NDB(I)-62 SN/OC 907(c)]. A study of the relationship between hemispheral and motor dominance is being conducted in collaboration with Dr. Baldwin.

Honors and Awards: None

Publications: None

---

[1] Reported to the New York Academy of Sciences meeting on the Use of Primates in Experimental Surgery, September, 1967.

Serial No. 3.9
1. Lab. of Applied Studies
2. Biomedical Studies Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Time Series Analysis Package

Previous Serial Number: Same

Principal Investigator: Raymond Mejia

Other Investigators: None

Cooperating Units: Computation and Data Processing Branch, DCRT

Man Years (computed for the 12 month period):

Total: 1.8
Professional: 1.3
Other (including computer time): 0.5

Project Description:

Objectives:

There has been a need at NIH for a library of computer programs to aid the analysis of time-dependent data. Benefits from such a set of programs will assure to the researcher who has collected small amounts of data over a relatively long period of time as well as to the project in which real-time data analysis is required to control physical or chemical processes.

A wide class of time series techniques has been implemented using the IBM 360/50 computer at NIH. These programs will be made available to remote users when such terminals are supported by the system.

Methods Employed:

A system of programs for the mathematical analysis of time series has been written, adapted for the NIH computing system and implemented under the current batch processing monitor.

Programs for "raw" data processing include the following:

a. acquisition of single channel and multiplexed data

b. probability density and joint probability density
c. decimation
d. normalization to zero mean and one standard deviation
e. test for linear trend and detrending
f. digital filtering and prewhitening.

Data generators for periodic, aperiodic and random data are available. Programs for correlation analysis include the following:

a. auto- and cross-covariance
b. auto- and cross-correlation
c. higher order correlations
d. lag windows including Parzen's, Bartlett's and Bram's.

Programs for frequency analysis include the following:

a. fast Fourier transform (SHARE routine PK FORT)
b. harmonic analysis
c. spectral and cross-spectral analysis
d. spectral windows including Hanning's and Daniell's
e. coherency between channels.

In addition to card input, data formats are accepted from the LINC computer operated by the Technical Development Section, NINDB, the DCRT 3100 hybrid computer and the SDS 910 digitizer at the Naval Ship Research and Development Center.

In addition to printed output, plots of desired quantities are provided using the DCRT Calcomp plotter.

Documentation in the form of a user's manual is currently in preparation and should be completed by the end of the Fiscal Year.

Significance to the Program of the Division:

The time series package serves as a tool in the analysis of data obtained during investigations undertaken within the Laboratory of Applied Studies and the other laboratories of the Division and the Institutes. It will facilitate the training of biomedical scientists in mathematical techniques which are applicable to their research, and in techniques which will facilitate the utilization of large-scale computation in their research programs.

Proposed Course of Project:

It is planned to continue to develop these programs in two directions. First, to accept problems which are currently too large to be processed by allowing for more input data (with more flexible input formats) in the available computer memory storage. Second, to serve a wider class of problems by adapting to the DCRT computing system when it permits remote utilization.

The optimization of calculations which are particularly time-consuming will be undertaken. The elimination of input parameters which are difficult to compute by the user is also desirable.

After testing and supervised utilization for some time, the package will be made available to other biomedical research activities.

Honors and Awards: None

Publications: None

Serial No. 3.10
1. Lab. of Applied Studies
2. Biomedical Studies Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Biological Model Evaluator Studies

Previous Serial Number: Same

Principal Investigator: John E. Fletcher

Co-Investigator: Richard Shrager

Cooperating Units: None

Man Years (computed for the 12 month period):

Total:	1.35
Professional:	1.25
Other:	.10

Project Description:

Objectives:

The object of the Biological Model Evaluator Studies is twofold. The primary object is to collect and develop those computer-oriented mathematical and statistical tools most applicable to the testing of biomathematic models. These tools are to be assimilated into user oriented program packages which provide NIH with a generalized biological model evaluator capability. Secondly, this project acts collaboratively in developing and supplementing mathematical-biological model building in other Institutes at NIH. In so doing, the requirements of biomedically oriented investigators for model evaluation are kept current and the capability of the evaluator programs can be updated accordingly.

Methods Employed:

1. The central concept of this project is model fitting by means of mathematical techniques. Two systems are currently operational. The first is the SAAM (Simulation Analysis and Modeling) system developed by the mathematical research branch of NIAMD, and the second is a nonlinear curve fitting program developed by Mr. Richard Shrager, Physical Sciences Laboratory, DCRT. The SAAM system is essentially a closed-package system of computer programs built

around the concept of compartmental analysis and its associated techniques. This system cannot be used in connection with other programs, and special modifications are necessary for all but a small class of well-defined mathematical models.

The second system is a class of generalized subroutines (NIHH22-23) designed to do nonlinear least squares curve fitting for a wide class of mathematical models. To use this system, a simple FORTRAN program is written defining the proposed model. The programming system accepts any model expressible in FORTRAN notation. In addition, it may be used as a subsystem in a larger user-oriented program. These newer, more versatile techniques are now documented and are being distributed for general NIH use. Further development of this project will permit the inclusion of data handling subroutines or numerical analysis subroutines which may enrich its utility as a biomedical tool.

2. Collaborative efforts are directed to the following projects:

NIH - NCI: Metabolism Branch; Dr. James Phang. The Quantitative Determination of Calcium Kinetics and Bone Synthesis in Normal Subjects, (Ending July 1, 1968).

NIH - NIMH - LCS: Unit on Psychosomatics; Dr. Leslie Baer. The Quantitative Determination of Sodium Kinetics in Normal and Diseased Patients. (Ended Jan. 1., 1968).

NIH - NHI: Section on Polypeptide Hormones, Laboratory of Molecular Disease; Dr. John Potts. Parathyroid Response to Changes in Serum Ca Level.

NIH - NHI: Section on Lipid Metabolism, Laboratory of Metabolism; Dr. Arthur Spector. Free Fatty Acid Transport and Utilization.

NIH - NCI: Laboratory of Biology; Dr. Fred Mushinski. Genetic and Biochemical Mechanisms Controlling Protein Synthesis in Well-Differentiated Neoplastic Cells, Mouse Plasma-Cell Tumors.

NIH - NIAMD: Laboratory of Physical Biology; Dr. Nobuko Kataoka and Dr. Hideo Kon. The Electron Spin Resonance of Low Spin Isocyanide Complexes of Co(II). I. Halides.

NIH - NIAMD - NHI: Laboratory of Physical Biology (NIAMD) and Laboratory of Biochemistry (NHI); Dr. Elliot Charney (NIAMD) and Dr. Lin Tsai (NHI). Spectral and Optical Activity of Conjugated Diketones.

NIH - NCI: Laboratory of Biochemistry; Dr. Herbert A. Sober. Optical Rotatory Dispersion Properties of Oligolysines.

These projects are discussed further in the reports of the respective Institutes. The participation in these efforts has involved basic formulation of an appropriate model for clinically acquired experimental data, data processing of the data and model, and interpretation of results. Refinements of the data collection, experimental methods, and biological models are often suggested as a consequence of mathematical results obtained through the computer program.

Proposed Course of Project:

Continuing efforts will (1) develop a library of special purpose models; (2) catalog supplementary subroutines which increase the utility of the model evaluator system; (3) document educational materials for training prospective users in mathematical-computer tools; and (4) provide collaborative and consulting efforts to selected NIH projects.

Honors and Awards: None

Publications:

Spector, Arthur A., and Fletcher, John E.: The binding of long-chain fatty acids to bovine serum albumin. J. Lipid Research. In press.

Shrager, Richard I., and Fletcher, John E. A User's Guide to Least Squares Model Building. DCRT Technical Report #1.

Serial No. 3.11
1. Lab. of Applied Studies
2. Stat. & Quan. Biol. Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Computer Simulation Methods and Related Statistical Methodology

Previous Serial Number: Same

Principal Investigators: Robert J. Connor, Dr. Eng.
Richard Greenstreet

Other Investigator: David VanSant

Cooperating Units: CDPB, DCRT

Man Years (computed for the 12 month period):

Total:	.96
Professional:	.85
Other:	.10

Project Description:

Objectives:

To provide NIH with special computer-related statistical models.

Major Findings:

1. A procedure for generating random samples from normal multivariate populations with specified mean vector and covariance matrix has been developed. It uses the random number generator reported in last year's Project Report Serial No. 3.11. It is programmed and available on system 360.

2. A discriminant function package has been developed to determine linear and quadratic discriminant functions for the two population case. Also, a non-parametric procedure for discrimination, based on order statistics, has been included (see Kendall[1]).

---

[1] Multivariate Analysis. Proc. of an International Symposium held in Dayton, Ohio, June 14-19, 1965. Edited by Paruchuri R. Krishnaiah, Academic Press, New York, 1966, pp. 165-185.

Currently, work is under way to investigate Kendall's procedure and some modifications of it.

A test for equality of covariance matrices has been programmed in BASIC for the time sharing units. It will be programmed for the 360 system in the near future and fully documented. The properties of this test are being investigated and much of the mathematical analysis essential for this investigation has been performed.

Honors and Awards: None

Publications: None

Serial No. 3.12
1. Lab. of Applied Studies
2. Biomedical Studies Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: EKG Modeling and Analysis

Previous Serial Number: Same

Principal Investigators: David B. Gilbert, M.D.
Robert E. Hackman, LAS, DCRT

Other Investigators: None

Cooperating Units: Surgical Branch, NHI (data alone)

Man Years (computed for the 12 month period):

Total:	0.5
Professional:	0.5
Other:	0.0

Project Description:

Objectives:

This year's efforts have been diverted to the technical problems of EKG analysis, specifically toward reducing the high data rates associated with the patient monitoring of electrocardiographic arrhythmias.

Methods Employed:

An algorithm was developed to characterize the uniqueness of a single QRST waveform when compared to a previous or standard complex. Combinations of the R-R interval and similarity of the waveform shape were compared with premature ventricular contractions, A-V block, nodal rhythms and sinus arrhythmias.

Major Findings:

Correlation coefficients in addition to R-R intervals appear to be a promising technique in reducing the high data rates associated with computerized monitoring of the EKG. Arrhythmias may be edited according to general mechanisms of pacing abnormalities and/or conduction abnormalities. Similar steady state normal or abnormal beats are deleted from the edited string. The algorithm as operated on the IBM 360/50 system operates better than real-time in FORTRAN IV.

Significance to Biomedical Research:

Present evidence points toward single heart beats as containing significant information in regard to acute myocardial infarction. Predictive algorithms of impending electrical failure must necessarily begin with optimal (every beat) analysis before decisions may be made as to the reliability of intermittent sampling. Economic computer every-beat analysis necessarily awaits an effective low-cost preprocessing system.

Proposed Course of Project:

A feasibility study will be made to determine whether the algorithm may be implemented in an 8K 1.5μ second cycle time desk-top machine. Both presently successful and future experimental algorithms will be simulated in 12- and 16-bit word form on the IBM 360/50. The overview will be to determine whether low-cost preprocessing of the EKG may be presently purchasable or fabricated within the Division.

Honors and Awards: None

Publications:

Gilbert, D.B., and Hackman, R.E.: A Data Reduction Technique for On-Line Arrhythmia Analysis. Abstract, Proceedings of the 3rd Joint Meeting, CSCOA, March, 1968.

Serial No. 3.13
1. Lab. of Applied Studies
2. Stat. & Quan. Biol. Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Statistical Analysis of Percentage or Proportional Data

Previous Serial Number: Same

Principal Investigator: James E. Mosimann, Ph.D.

Other Investigators: Robert J. Connor, Dr. Eng.

Cooperating Units: None

Man Years (computed for the 12 month period):

Total:	.87
Professional:	.67
Other:	.20

Project Description:

Objectives and Methods:

1. To provide mathematical and statistical models to permit the analysis of data which are proportioned, e.g., per cent serum protein constituents of blood.

2. To provide mathematical support for biological studies of growth and differential growth. The primary mathematical methods involved are those of probability and mathematical statistics along the lines of the multivariate beta or Dirichlet model (Mosimann, 1962, 1963).

Major Findings:

Definitions of independence for proportions are developed. A general class of multivariate distribution whose variables meet the definitions has been developed. The general class describes a competitive situation in which one particular proportion has a dominant role to some other proportions. This means, for example, that one variable assumes its share of a resource without reference to the amount the second variable then subsequently assumes. The models include as a special case the Dirichlet model. Hence, they provide alternative hypotheses to the simpler non-competitive hypothesis associated with the Dirichlet model. In analyzing data on differential growth published by Mosimann, the models have proved to be of biological use in identifying which of several variables shows growth dominant to other variables. Data on bone composition of rats has been analyzed. These data are included in a paper "Concepts of Independence for Proportions with a Generalization of the Dirichlet Distribution" which has been completed and submitted for publication.

References:

1962. On the compound multinomial distribution, the multivariate beta distribution and correlations among proportions. Biometrika. Vol. 49, No. 1-2, p. 65-82.

1963. On the compound negative multinomial distribution and correlations among inversely sampled pollen counts. Biometrika. p. 47-54.

Honors and Awards: None

Publications: None

Serial No. 3.14
1. Lab. of Applied Studies
2. Stat. & Quan. Biol. Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A Range Distribution and Related Tests for Homogeneity

Previous Serial Number: None

Principal Investigator: Robert J. Connor, Dr. Eng.

Cooperating Units: None

Man Years (computed for the 12 month period):

Total:	.17
Professional:	.12
Other:	.05

Project Description:

Objectives:

To provide NIH scientists with statistical methodology for testing the homogeneity of events on a discrete scale (or over classes).

Major Findings:

The distribution of the sample range from a finite discrete rectangular distribution has been derived. Utilizing this result a non-parametric test for homogeneity over a discrete scale has been developed and studied. It has been found that this test when used in conjunction with the Kolmogorov-Smirnov test is of considerable value, being sensitive to situations at boundaries of classes.

Honors and Awards: None

Publications: None

Serial No. 3.15
1. Lab. of Applied Studies
2. Stat. & Quan. Biol. Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Interview Scheduling for Clinical, Research and Staff Associate Applicants

Previous Serial Number: Same

Principal Investigator: Frank A. Petro, Jr.

Other Investigators: James E. Mosimann, Ph.D.

Cooperating Units: Clinical and Professional Education Section, Clinical Center

Man Years (computed for the 12 month period):

Total:	2.00
Professional:	1.75
Other:	0.25

Project Description:

Objectives:

1. To automate interview scheduling for, and subsequent assignment of, clinical, staff and research associate applicants.

2. To develop mathematical algorithms to permit automatic scheduling and assignment by the System 360.

Methods Employed:

1. Matrix algebra and linear programming were used to develop the underlying mathematics.

2. Computer methods required to use the disc and tape of System 360.

Major Finding:

The scheduling algorithm has been developed. The mathematical consequences of the algorithm have been demonstrated and are known.

Proposed Course of Project:

The scheduling system is fully implemented. It replaced the manual system in January, 1968.

Honors and Awards: None

Publications: None

Serial No. 3.16
1. Lab. of Applied Studies
2. Office of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Signal-Noise Relationships in Neuroelectric Data

Previous Serial Number: Same

Principal Investigators: Eugene K. Harris, Ph.D., DCRT
Charles D. Woody, M.D., NIMH

Cooperating Units: Laboratory of Neurophysiology, NIMH

Man Years (computed for the 12 month period):

Total:	0.6
Professional:	0.6
Other:	0.0

Project Description:

Objectives:

To characterize band-limited noise components of neuroelectric signals and, in particular, to distinguish signal-associated from signal-unassociated components of such noise, with expectation that this discrimination will aid in understanding the statistical organization of adaptive neural systems.

Methods Employed:

A method has been developed (by C.D. Woody) for recovering signal waveforms from background noise by means of an adaptive filter technique using an iterative correlation-averaging procedure. With each iteration, peak crosscorrelations between template and replicate samples determine re-alignment of signals, followed by averaging to produce improved signal in the template record. After each cycle, a computer program provides display of the frequency distribution of deviations of sample waveforms from complete convergence. The average peak crosscorrelation is also computed. Parameters of these frequency distributions, together with observed correlation coefficients represent potential tools for distinguishing signal-associated from signal-unassociated band-limited noise components. Experiments have been performed using both artificial and neuroelectric signals.

The former have been time-locked signals of two different waveforms in noise of varying bandwidths, over a wide range of signal/noise ratios. Noise generation, signal insertion and adaptive filtering have all been performed digitally on the IBM 360/50 computer.

Major Findings:

Results obtained during the present reporting period show conclusively that the capability exists, essentially independent of signal waveform, to quantify signal-associated noise components in neuroelectric signals, and to estimate pre-filtered signal/noise levels, through statistical analysis of computer output from adaptive filtering.

Significance to Biomedical Research:

These results provide simple, useful tools for describing dynamic changes in the organization of specific neural systems as monitored by extracellular deep electrodes during processes of sensory stimulation, habituation and conditioning.

Proposed Course of Project:

(1) Further experimentation with neuroelectric signals in cats under various behavioral regimens; (2) computer studies of artificial, variable-latency signals to determine the feasibility of estimating the distribution of latencies by application of mathematical models to output from adaptive filtering.

Honors and Awards: None

Publications:

Woody, Charles D.: Characterization of an adaptive filter for the analysis of variable latency neuroelectric signals. Med. and Biol. Eng. 5: 539-553, 1967.

July 1, 1967 through June 30, 1968

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities	1. DCRT - 4 Serial Number
2. COMPUTER SYSTEMS LABORATORY	3. Alan Demmerle Acting Chief

I. SUMMARY

This Laboratory, now in its second year of operation, is currently pursuing three broad objectives in support of the conviction that computer technology can make substantial contributions to biomedical research in ways other than conventional data processing. These objectives are the development of processing systems for laboratory and clinical data, the development of data processing techniques, and the development of new applications for computers. The projects through which this Laboratory is pursuing these objectives include the design and development of computer systems to collect and manipulate data and control experiments in real time, systems for off-line data collection, a hybrid (analog/digital) computing facility, components of information retrieval systems, and other generally new applications of computers. All of these programs show great promise.

II. CURRENT LABORATORY PROGRAMS

The Computer Systems Laboratory, now in its second year of existence, has continued toward the system-oriented goals which it established last year. It has grown in size by about one third, and is now composed of 33 individuals representing the disciplines of engineering, mathematics, linguistics, and medicine, but who could be appropriately called Information System Specialists. Some of the projects started during the previous reporting period have carried over into this one; a few have been deferred, and many new ones have been undertaken.

A. Objectives

The objectives reported last year have not changed in substance, although the scope has been broadened. In order to see these objectives in a new perspective, they are set forth here in a different way from last year.

The Laboratory is dedicated to three broad objectives:

1. The development of processing systems for laboratory and clinical data
    a. Through the use of separate, dedicated, general-purpose computer systems

   b. Through data collection systems for use in conjunction with a central computing facility

   c. Through the use of special-purpose, hard-wired data processors.

2. Research, development, and implementation of new data processing techniques emphasizing the aspects of:

   a. Methodology

   b. Systems

   c. Hardware

   d. Software

3. Development and implementation of new applications for computers

The manner in which these objectives have been pursued through projects is summarized below.

B. Progress

The objectives previously set forth represent the current broad goals of this Laboratory. A number of projects have been undertaken in pursuit of each of these objectives. These projects, grouped under their general objectives, are briefly reviewed below. More details for many of the projects are included as Individual Project Reports.

Progress Toward Objective 1 (Development of processing systems for laboratory and clinical data)

There remain many project areas at NIH in which the use of a computer as a tool has not yet been explored or exploited. The laboratory and the clinical environment are particularly fertile areas in which computer technology can be applied. To date, however, our concentration has been primarily in the laboratory environment. It is our intention to help uncover project areas in both environments, and, by working in cooperation with the scientists involved, design systems to meet the data processing requirements of these project areas. The term "data processing" is to be considered in its broadest sense, and includes the collection, manipulation, computation, and display of data. These data processing requirements tend to fall into three categories:

   a. Those requiring the full support of a general-purpose computer system at the site because of the size and complexity of the requirement or the number of requirements in a limited vicinity, or the requirement for "real-time" processing of data and process control.

b. Those requiring data collection (and possibly display and transmission) for analysis, possibly at some later time, at some computing facility remote from the source of the data.

c. Those requiring specific processing which can be most economically implemented by hard-wired systems.

We have examined several project areas at NIH, determined the category prescribed by the requirements, and designed systems to meet these requirements.

1. a. We have designed, and are currently purchasing, a single computer system to serve all of the laboratories in NIDR jointly (described in detail in the Individual Project Report, DCRT 4.1). Similarly, we have designed, and are now purchasing, two other complete computer systems, one for some of the biochemical laboratories of NIAMD, and one for the Mass Spectrometer systems of LM, NHI (described in detail in the Individual Project Reports, DCRT 4.10 and 4.11). We have also designed three other complete computer systems, one to meet the needs of the NIMH scientists in Building 10 (DCRT 4.23), one for the Gerontology Branch of NICHHD, Baltimore (DCRT 4.24), and one for the Section on Comparative Behavior, NIMH, Poolesville (DCRT 4.25). These latter three systems, optimally designed to meet the specific needs of these groups, have not yet reached the procurement stage. All six systems are composed, in part, of commercially available equipment and software which will be purchased, and in part by non-available equipment and software which will be designed and implemented in this Laboratory. When implemented, these systems will represent a significant advance in the application of computation to biology and medicine. The systems will, in general, be used for collecting and analyzing data in real-time by having instruments directly connected to the computer; controlling experiments while they are being conducted; and developing new ways to do experiments which become possible only by virtue of the computational power of the computer.

In addition, of course, these systems will serve the traditional function of analyzing experimental data that has been collected. In addition to the system design, this Laboratory has assumed primary responsibility for achieving successful system operation. This involves developing the interface between the instruments and the computer, implementing remote communication links, and developing the applications and system controlling software. The systems will then, for the most part, be turned over to the scientists who expect to use them. In the final analysis, the value of these systems depends upon the laboratory scientists learning to use the computer as a tool since a fundamental appreciation of its capability is necessary if it is to continue to be used in an innovative way.

In addition to the actual design of computer systems for use at NIH, we have provided consultation on the design and use of computer systems for extramural programs, particularly to NHI and to NIMH. The largest user of our expertise in this area was the NHI, whom we have helped on a continuing basis, particularly with the data management portion of the Myocardial Infarction Research Unit program. This is described in greater detail in Individual Project Report DCRT 4.12.

1. b. In some of the laboratories whose data processing requirements have been analyzed, complete computer systems are inappropriate at this time. In LM and LTD of NHI, and MET of NCI, we found that collection of data on digital magnetic tape, analog magnetic tape, and punched paper tape, respectively, and analysis of this data at a central facility was the best solution of their data processing requirements. These recommendations have not been acted upon to date. These cases are reported on in greater detail in the Individual Project Report DCRT 4.13.

For general use with such off-line data recording systems, we are developing time and event code generators and decoders. These allow the user of an automated data collection system to keep better track of the relationship between his experiment and his data. The generator will be used at the source of the data recording, and the decoder will be used at the site of the data processing. These units are described in greater detail in Individual Project Report DCRT 4.14.

1. c. Data processing requirements can sometimes be best met by special purpose computing systems, as opposed to the general purpose computers that we think of when we hear the word "computer." The special purpose systems, as the name implies, are designed for a specific job, and the logic is generally wired, although sometimes through a patchboard, so that they are not as easily adapted to other jobs as a stored program general purpose computer. They have a definite economic advantage when a single well-defined function is to be done repetitively. There are many uses for such machines at NIH. The monitoring of critically ill patients is one such area where these machines will be used in conjunction with general purpose machines. This Laboratory is currently developing such a special purpose computer for ECG analysis. The algorithms for the analysis were developed on this Laboratory's CDC 3100 computer system. Special purpose hardware, using these software algorithms, was then designed, and provides for a faster and more economical beat-to-beat ECG analysis than would be possible with a general purpose computer system. The end result is small, portable equipment for continuous real-time analysis of ECG data at the bedside. This is described in greater detail in the Individual Project Report DCRT 4.15.

Progress Toward Objective 2 (Research, development, and implementation of new data processing techniques)

We have pursued this goal in four general areas.

a. Methodology - We are developing ideas relating to the organization of computing and memory systems. These ideas are quite imaginative, and their utility is under evaluation. They are described in the Individual Project Report DCRT 4.16.

b. Systems - The Hybrid Computer System (located in Building 10), after a fretful infancy, now offers hybrid computation, analog computation, digital computation, and analog to digital conversion. It is used currently nearly to capacity, and, hence, we are expanding its capability through the addition of a disk and a higher speed printer. To date, this system has been used mostly for standard digital computation rather than for hybrid computation. The hybrid computer provides a powerful tool for the solution of biomedical problems which involve biological systems modeling and simulation. The demand for this type of work has not met expectations, and problems requiring collaborative work in this area are being solicited. The work that has been done with this system is reported in some detail in the Individual Project Report DCRT 4.9.

c. Hardware - The nature of some data renders present data processing techniques uneconomical. As an example, data which, for short periods, are actively changing, but, for the rest of the time do not change, keep a computer system, or, at least, an input channel, busy all the time. We are developing "data compression" techniques to remedy this problem. These techniques will be implemented, probably with hardware external to the computer, in situations where the computer can be more productively used during periods of inactive data. This project is described in Individual Project Report DCRT 4.17.

d. Software - The processing, particularly searching and up-dating of large, active files of data, has, traditionally, led to long, complicated, and inefficient computer programs. New techniques leading to new software packages have been developed to minimize these problems, and are discussed in the Individual Project Report DCRT 4.18.

Progress Toward Objective 3 (Development and implementation of new applications for computers)

This objective, which overlaps Objective 1, due to its broadness, is an extremely important part of the mission of this Laboratory and Division. We have pursued this goal through several projects. We are currently working on a project which will lead to both the automatic abstracting of textual data and to better information retrieval systems. Key information, abstracted with the use of a computer doing linguistic analysis of autopsy reports, currently provides an input data source for a pathology data retrieval system. It will be extended for use in information retrieval systems using other types of medical textual data. The expectations and methods of this project are more thoroughly described in the Individual Project Report DCRT 4.19.

Another project which holds great promise is one to develop the methodology whereby the potential of the computer is made available in the physician's office at a reasonable cost. Such a system would permit access to the memory and computational abilities of a computer to relate symptoms to diseases and to compute treatment protocols for burn patients, etc. This fascinating application is discussed more fully in the Individual Project Report DCRT 4.20. Other applications of computation which have been pursued primarily through collaboration with other institutes include the Analysis of Laboratory Spectral Data, the Determination of Sequences of Protein and Nucleic Acids, the Analysis of Bone Density Measurements, and some work involving the small computer, called the Programmed Console, used in Radiation Therapy in the Clinical Center. These projects are reported on in the Individual Project Reports, DCRT 4.21, 4.5, 4.22, and 4.8, respectively.

General Remarks

In general, support available for the projects which have been discussed has been adequate, particularly with regard to finances, personnel resources, and enthusiasm from the management involved. However, space available to house personnel on the projects, and to house the electronics laboratory used in support of these projects has been totally inadequate. This has been detrimental to our programs. The members of this Laboratory look forward to the fulfillment of promises for more space.

There are a number of other projects, particularly in the clinical area, which could, and should, be undertaken, and which have the moral support of the management involved, but which cannot be undertaken now, or in the near future, without additional staff. Many projects in the computer system business cannot be undertaken halfheartedly since they require a substantial effort over an extended period of time to assure their success. Inadequate financial support and personnel would undoubtedly lead to failure of these projects.

Serial No. DCRT 4.1
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Dental Institute Computing System

Previous Serial Number: DCRT 4.1

Principal Investigator: Daniel Syed

Other Investigators: William Holsinger

Cooperating Units: National Institute of Dental Research

Man Years:

Total: .5
Professional: .5
Other: 0

Project Description:

Objectives:

This project is intended to provide on-line real-time computational support for the biochemistry and neurophysiology research programs of the National Institute of Dental Research. The computer system is designed to automate data acquisition from instruments in the biochemistry laboratories, to perform limited computations on captured data, and eventually to control experiments. During neurophysiological research procedures, the system will provide information relative to the proper placement of electrodes, pertinent waveforms enhanced by averaging techniques to improve signal-to-noise ratios, and correlative relationships. The system will provide a test bed for the development of hardware and software techniques for automating many instruments that have not been automated on even an off-line basis.

Methods:

The analysis and system specifications were submitted through departmental channels to obtain data processing clearance. Considerable delay was encountered due to DHEW reorganization. Program approval was received in February, at which time a request for proposal was released. Responses to this request for proposal are being evaluated.

Major Findings: None

Significance to Biomedical Research and the Program of DCRT:

The proposed system will permit this Division to develop software and hardware for use in similar applications around the campus. Such a system will be used as a research tool in the design of an optimal system for biomedical applications stressing data acquisition. Consistent with the development of time-sharing software on the Central Computer Facility IBM 360/50, the system will provide a basis for analysis and development of satellite computing techniques in a biomedical environment.

Proposed Course:

Upon selection of a specific manufacturer and negotiation of an acceptable contract, special purpose hardware for interfacing the instruments with the selected computer will be developed. Associated software for support of research programs in real-time, including substantial modifications to a real time monitor, will be developed concurrently.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.3
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Study of Hybrid Computer Utilization in Support of Laboratory of Metabolism, NHI

Previous Serial Number: DCRT 4.3

Principal Investigator: Daniel Syed

Other Investigators: William Holsinger

Cooperating Units: None

Man Years:

Total: 0
Professional: 0
Other: 0

Project Description:

Objectives:

This study was designed to investigate the feasibility of expanding the current hybrid configuration to support biochemistry research programs of the Laboratory of Metabolism, National Heart Institute. Since the cost of modification of the hybrid facility was considered prohibitive and the alternate methods were not considered acceptable, the project was terminated.

Methods Employed: None

Major Findings: None

Significance to Biomedical Research and the Program of DCRT: None

Proposed Course: None

Honors and Awards: None

Publications: None

Serial No. DCRT 4.4
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Hospital Patient Record and Information and Retrieval System

Previous Serial Number: DCRT 4.4

Principal Investigator: Victor Colburn

Other Investigators: William White, Michael Otten

Cooperating Units: None

Man Years:

Total: 1.2
Professional: 1.2
Other: 0

Project Description:

Objectives:

Early in fiscal 1968, the previously reported objectives of this project were shifted to include procurement and implementation of a general-purpose computer display facility. The previous objectives involved a planned approach to application of computer system technology within the NIH Clinical Center. These earlier objectives remain intact, with the intention that they will constitute a primary use of the proposed new Computer Display Facility.

Methods Employed:

The major activity on this project during fiscal 1968 consisted of the preparation of a functional specification suitable for normal RFP procedures.

Major Findings:

A specification for a real-time Computer Display Facility was completed at about mid-year fiscal 1968. The specification provides for a multi-user time-shared facility with up to 66 remote terminals, including cathode-ray tube displays of both character type and the more sophisticated graphic varieties. Terminals will contain keyboards and machine readers for control and data inputs. There is provision for automatic input of data from bio-medical and laboratory instrumentation. The facility will include a mass storage system. Strong emphasis is placed on interactive operation and user convenience.

Further effort was curtailed at this point, due primarily to budget cuts occurring at about midyear fiscal 1968, coupled with lack of a hard requirement for such a computer facility, for example, strong justification from an existing project outside of DCRT. However, portions of the above-mentioned specifications are being used for procurement of a computer system for Pharmacology and Toxicology, in a collaborative effort between DRFR and DCRT.

There is little purpose in the further pursuit of the originally stated objectives of this project, until procurement of such a computer display facility can be reactivated.

Significance to Biomedical Research and the Program of DCRT:

The procurement by DCRT of the proposed general purpose real-time computer display facility still appears to be a worthy objective. We are convinced that when such a facility is available, it will find much application. Many computer applications now implemented on teletype remote service will find new life in the much greater speed and flexibility of the proposed facility.

Proposed Course of Project:

The project is currently dormant due to lack of funds. If adequate funds can be allocated within the next 1 to 2 year period, it should probably be reactivated, without significant change.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.5
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Sequence Determination of Proteins and Nucleic Acids

Previous Serial Number: 4.5

Principal Investigator: Marvin Shapiro

Other Investigators: Jay Vinton, Lewis Sheiner, Carl Merril

Cooperating Units: Laboratory of Neurochemistry, NIMH; Laboratory of General and Comparative Biochemistry, NIMH

Man Years:

Total: 1
Professional: 1
Other: 0

Project Description:

Objectives:

(1) The mathematical reconstruction of protein and RNA sequences from laboratory data and (2) the computer simulation of the laboratory process of sequencing a biopolymer.

Methods Employed:

The development of an algorithm for reconstructing sequences and the use of this algorithm in a program which simulated the steps followed in the laboratory sequencing of an RNA molecule.

Major Findings:

The simulation program was completed. Different sets of laboratory conditions were postulated (including sequence size and composition, amount and types of equipment available, and laboratory personnel available) and computer runs were made.

Significance to Biomedical Research and the Program of DCRT:

(1) The sequencing process was formalized.
(2) Computer results indicated bottlenecks in the process due to

lack of essential equipment or personnel and gave estimates of the time needed to sequence RNA polymers of prescribed lengths and compositions.

Proposed Course:

Further computer runs will be made to obtain further information and statistics in order to gain insight into the sequencing problem. Possible modifications will be made in the program to make the simulation more accurate.

Honors and Awards: None

Publications:

Shapiro, M. B.: An Algorithm for Reconstructing Protein and RNA Sequences. J. Assoc. Computing Mach. 14, 720-731, October, 1967

Serial No. DCRT 4.8
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Support of Programmed Console

Previous Serial Number: 4.8

Principal Investigator: William White

Other Investigators: None

Cooperating Units: Radiation Branch, NCI

Man Years:

Professional: .2
Other: 0
Total: .2

Project Description:

Objectives:

Continuing support for the use of the programmed console has included consultation, suggestions for hardware addition, and the programming of an assembler for the program console symbolic language.

Methods Employed:

A program written in PL/1 for the 360/50 accepts the symbolic machine language of the Spear PC, and produces a bit pattern in 12 bit words which is an "object program" for the Programmed Console. The PL/1 program produces a listing containing the address in decimal and octal, and the instruction in binary, octal, and symbolic.

Major Findings:

The assembler appears to be a useful addition to the software of the Programmed Console. The experience of writing this type of program in PL/1 demonstrates the utility of the PL/1 language, and suggests other similar conversion applications.

Significance to Biomedical Research and the Program of DCRT:

The use of small special-purpose computers in research projects and patient care situations offers the advantages of immediate access, fast response, and the ability of the investigator to interact with his program and the computer. The limitations of size, storage capability, and versatility of the small computer can be surmounted by support from, and communication with, the larger NIH computer facility.

Proposed Course:

It is proposed that a direct communication link from the 360/50 system to the Programmed Console be established as soon as feasible. When this is accomplished, the assembler program will have the capability of loading a program directly into the Programmed Console. Other support activities will involve the programming for cataloging and storing programs and data from the Programmed Console in the 360/50 system and the development of additional software such as a FORTRAN compiler for the Programmed Console.

Honors and Awards: None

Publications: None

Serial No. DCRT - 4.9
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Hybrid Computer Project

Previous Serial Number: Same

Principal Investigator: Perry S. Plexico

Other Investigators: Leroy Brown, S. J. Farlow, Robert Romanoff,
David Songco, Philip Turner

Cooperating Units: Section on Clinical Biophysics, Cardiology Branch, NHI

Man Years:

Total:	4.7
Professional:	3.7
Other:	1

Project Description:

Objectives:

1. To develop a hybrid analog/digital computer system and methods of applying it to the simulation and modeling of biological systems.

2. To provide methods and capability for data conversion, editing, and real-time analysis.

Methods Employed:

Mathematical techniques for the optimization and correlation of models of biological systems to experimental data have been developed, and computer programs written to execute these techniques on the hybrid computer. Software was completed to accomplish real-time data conversion and editing, and to allow the use of FORTRAN for certain classes of real-time data analysis.

Major Findings:

Efforts to correct the serious engineering design problems which existed in the analog computer and linkage portions of the hybrid system were continued, with the result that the system was brought to full operational status in August 1967. Sample-and-hold amplifiers to be used as an aid to data conversion were designed and completed in May, 1968.

As a test of the hybrid optimization techniques which were developed, a number of test problems were executed. These same problems were repeated using a strictly digital computer method, wherein the analog computer was digitally simulated. Results of these tests were in close agreement, but the hybrid implementation had a speed advantage of several thousand to one over the digital method. Following these tests, a mathematical model of cardiac muscle was simulated on the hybrid computer, and an attempt made to correlate it with experimental data using a gradient optimization procedure. While a reasonable correlation was not obtained, the detailed study of the model made necessary during the optimization attempt revealed several features in its mathematical formulation which violated the original hypotheses on which it was based.

Significance to Biomedical Research and the Program of DCRT:

1. The hybrid computer was shown to be of significant value for the simulation and modeling of biological systems which may be mathematically expressed in terms of differential equations.

2. A number of investigators from several Institutes and Divisions have been informally trained in the use of the hybrid system and have applied it to a variety of scientific computation tasks.

3. At this time, the hybrid computer offers the only data conversion and real-time data analysis facility available on an NIH-wide basis. The capability of applying the FORTRAN programming language for certain of these functions greatly simplifies its use.

Proposed Course of Project:

1. Efforts of this project will continue to be directed to the simulation and modeling of biological systems. Problems currently under consideration include in vivo studies of pulsatile blood flow, fluid flow through collapsible tubes (of significance in both pulmonary and vascular mechanics), and optimal muscle control.

2. The digital portion of the system is to be expanded to include mass data storage capability and a higher speed printer which will substantially improve the system's operating efficiency. It is the intent of this project to further utilize this increased capability to perform research in multi-programming and time-sharing, hopefully including the processing of real-time laboratory data from remote locations.

Honors and Awards: None

Publications:

Plexico, Perry S.: Multiparameter Optimization of Dynamic Systems Using a Hybrid Computer. M.S. Thesis, George Washington University, February, 1968.

Serial No. DCRT - 4.10
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Computer System for Biochemical Laboratories of NIAMD

Previous Serial Number: None

Principal Investigator: Marvin Shapiro

Other Investigators: Jeffrey Buzen, Isaac Hantman, Kenneth Kempner, Arthur Schultz, Jay Vinton

Cooperating Units: Laboratories of Physical Biology and Molecular Biology, NIAMD

Man Years:

Total: 2
Professional: 2
Other: 0

Project Description:

Objectives:

To develop a real-time data acquisition and analysis computer system to service the laboratories in Building 2, NIAMD.

Methods Employed:

The computational needs of a representative group of scientists in Building 2 were examined from the standpoint of equipment used, data rates, methods of data analysis, and possible application of feedback methods.

Major Findings:

Specifications were written for a real-time computer system for Building 2, and a request for proposals was prepared.

Significance to Biomedical Research and the Program of DCRT:

Implementation of the proposed computer system would have far-reaching implications: (1) Present turn-around time for computer results in Building 2 would change from days to minutes. (2) Close interaction between scientist and computer would make new methods of data analysis possible. (3) Real-time data collection would give more accurate results than are now obtainable. (4) The on-line system would be far more flexible and accessible than the current batch processing use of the remotely located IBM 360/50 computer.

Proposed Course of Project:

A computer will be selected, and programs will be written to accomplish acquisition and analysis of data from instruments interfaced directly with the computer.

Honors and Awards: None

Publications: None

Serial No. DCRT - 4.11
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Computer Applications to Mass Spectrometer Data

Previous Serial Number: None

Principal Investigator: Eli Gilbert

Other Investigators: Henry Fales, George W. Milne, Jay Vinton

Cooperating Units: Laboratory of Metabolism, NHI

Man Years:

Total:	1
Professional:	1
Other:	0

Project Description:

Objectives:

To develop a computer system for reducing data produced by a mass spectrometer and computer programs for further analyzing the data to give insights into the topological structure of complex molecules.

Methods Employed:

Specifications were developed for a computer system to be directly connected to Dr. Fales' mass spectrometers. The system will accept data in real-time and perform some data reduction. Programs were completed for the IBM 360/50 and Hybrid computers, to handle (1) digitization of raw data (2) recognition of peaks (3) standardization of peaks and (4) calculation, for each peak, of a centroid, area, and empirical molecular formula. In addition, plotter routines were written for displaying the possible paths followed by the molecule in fragmenting.

Major Findings:

A rapid turnaround system was implemented for mass spectrometer data. Data so reduced will be used as the basis for the application of heuristic methods in molecular structure determinations.

Significance to Biomedical Research and the Program of DCRT:

Through use of the computer, a significant increase in the amount of mass spectrometer data analyzed was realized. In addition, some of the computer output, notably the plotter results, provided new insights into the underlying molecular structures.

Proposed Course of Project:

(1) Analysis programs will be completed. (2) A large effort has begun toward applying heuristic methods to structure determination and (3) a small real-time computer system has been requested, to be directly connected to the mass spectrometer. Its implementation will increase the overall data throughput rate of the current system by an order of magnitude.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.12
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Data Management Systems for the Myocardial Infarction Research Unit Program

Previous Serial Number: None

Principal Investigator: Daniel Syed

Other Investigators: Kenneth Kempner

Cooperating Units: None

Man Years:

Total: .25
Professional: .25
Other: 0

Project Description:

Objectives:

Five institutions have been funded by the National Heart Institute to study the causes and characteristics of myocardial infarction. This research program, it is hoped, will lead to improved techniques in both the prevention and treatment of this disease. This project is intended to provide guidance in the establishment of individual data management systems to the five myocardial infarction research units already funded, and to the seven additional institutions scheduled to receive funds. A primary goal is to promote compatibility of hardware and software to the maximum extent possible. A secondary objective is the assimilation of "state of the art" techniques in cardiac monitoring in preparation for the design of a computer system for the recovery area of the Clinical Center heart surgical suite.

Methods Employed:

Guidance to the myocardial infarction research units is accomplished primarily through consultation provided to the National Heart Institute. Although the computation and data management plans of each institution involved have been reviewed and have frequently resulted in major recommendations, a most important facet of the project has been the opportunity to visit and evaluate personally several leading non-MIRU institutions engaged in cardiovascular research, all the MIRU institutions thus far funded, and also many of the leading computer manufacturers that rank as potential MIRU contractors. It is this facet, in fact, which has made it possible for DCRT to offer some tangible guidelines and goals to the National Heart Institute, independent of submissions from the selected myocardial infarction research units.

Major Findings: None

Significance to Biomedical Research and the Program of DCRT:

This project provides a basis for evaluating the feasibility of attempting collaboration between institutions establishing individual data management systems directed toward a similar goal. It will also provide experience in cardiac monitoring and care. This experience will be invaluable in prosecuting projects within the heart surgical suite in the Clinical Center.

Proposed Course:

Consultation to the National Heart Institute in the area of the establishment of data management systems will continue. Eventually, this consultation will be extended to include guidance in the analysis of data acquired by the various institutions involved.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.13
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Special Purpose Data Processing Systems for NHI and NCI

Previous Serial Number: None

Principal Investigator: Paul Heffner

Other Investigators: David Songco

Cooperating Units: (1) Laboratory of Metabolism, NHI
(2) Laboratory of Technical Development, NHI
(3) Metabolism Branch, NCI

Man Years:

Professional: .75
Other: 0
Total: .75

Project Description:

Objectives:

To analyze laboratory data collection requirements, and design the appropriate system to collect and prepare the data from these laboratories for computer analysis.

Methods Employed:

During this reporting period, the computing requirements of three laboratories were analyzed. The most effective and economical approach to these requirements was through off-line collection of data which is then manually transported to a computer system. Each system is summarized below.

1) Laboratory of Metabolism, NHI
There are several gas and liquid chromatograph instruments in this laboratory, the data from which requires analysis. This data can be best collected on a unified data storage system whereby the data from each instrument would be multiplexed on to a single digital magnetic tape. Once a day this tape could be taken to a computer center where it would be processed, and the results available to the experimenters in less than 24 hours from the initiation of the experiment. The computer would

calculate the corrected areas under peaks, and locate the centers of the peaks with respect to calibration runs.

2) Laboratory of Technical Development, NHI
Several particle-detecting instruments are used to make measurements of the growth of organisms which are captured in an agar media. A data storage medium is required to collect data from the above experiment and to transport it to a computer system. Software is required to calculate pulse height and pulse width distributions associated with the detection of the particles. An analog tape recording system was recommended.

3) Metabolism Branch, NCI
Five liquid and crystal scintillation systems produce data which is currently analyzed manually. A paper tape system for data collection, formatting, and storage would allow for statistical analysis of this data on a computer system. Programming is required to perform the analysis and to present the results in printed form and on punched cards.

Major Findings:

The advantage common to each system is that it reduces to a minimum the tedious and time-consuming hand calculations that are presently performed in processing the raw data. Secondly, the accuracies that will be afforded by the computerized techniques will exceed those of hand calculation.

Significance to Biomedical Research and the Program of DCRT:

In reducing the time required by the researcher to process his data, more time will be available to him to extend his investigations. Further, the computerized analyses can provide additional information about the data through algorithms too involved for repetitious hand calculations, and can remove deleterious data from calculations.

Proposed Course of Project:

If these systems are acceptable to the management of the laboratories concerned, CSL could oversee their implementation.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.14
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Combined Event and Time Code Generator and Reader Units

Previous Serial Number: None

Principal Investigators: Paul Heffner - David Songco

Other Investigators: None

Cooperating Units: None

Man Years:

Total: .5
Professional: .5
Other: 0

Project Description:

Objectives:

The objective of this project is to make a time and event code generator available to NIH experimenters who record their test data on analog tapes. By combining both an event encoder and decoder and a precision time code generator and reader into one compact unit, an optimal capability for the marking of recorded experimental data will be effected.

Methods Employed:

Functionally, the event code generator will place a manually programmed identification code on the carrier of a modified IRIG B BCD time code, in addition to the time code, so that the time code continuity will not be disrupted when an event is marked. Time will be resolved in seconds, minutes, and hours, and will be accurate to better than .002%. The day of year count can, in addition, be placed in the code if the operator so chooses. The decoding capability of the unit will enable an experimenter to play back his data from his recorded magnetic tape and to relocate a pre-programmed part of his experiment. In addition, the unit will be made compatible with the CDC 3100 computer in Building 10 for automatic location of experimental data during the processing of recorded data, and to enable computer entry of the absolute time upon computer request. The system has been designed to employ integrated circuits primarily.

Major Findings: None

Significance to Biomedical Research and the Program of DCRT:

The availability of a precision time code signal during the recording of experimental data will enable the experimenter to reconstitute time along with his data during later processing of the recorded experiment. The signal will also enable an experimenter to evaluate his own recording and reproducing process with regard to both dynamic and static playback tape speed errors. For archiving purposes, the time code can log the time and day of year of the test as a permanent record on the tape.

Proposed Course:

The first four units are expected to be completed by the Fall of 1968. If more units are desired by experimenters, the Computer Systems Laboratory can oversee their fabrication.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.15
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Beat-to-Beat ECG Analysis

Previous Serial Number: None

Principal Investigator: Daniel Syed

Other Investigators: Kenneth Kempner, Martin Miller, William Holsinger

Cooperating Units: None

Man Years:

Total: .75
Professional: .75
Other: 0

Project Description:

Objectives:

The primary objective of this research program is the development of real time ECG rhythm analysis techniques for the detection and classification of cardiac arrhythmias. Milestones in this program are the identification of parameters which will differentiate between the most commonly occurring arrhythmias and the development of computer software and hardware systems for the acquisition and reduction of the ECG waveform.

Methods Employed:

In the area of computer software, several programs have been developed which allow the detection of R waves, computation of R-R interval Histograms, and the calculation of the correlation coefficient and RMS error between two ECG complexes. These computations are accomplished in better than real time using a data set of representative arrhythmias stored on magnetic tape. The criteria developed for the detection of the QRS complex is insensitive to the presence of baseline drift and noise.

A special purpose digital system has been designed as the hardware counterpart of the software system. This equipment is expected to perform the arrhythmia detection and classification without the support of a general purpose, stored program digital computer.

Major Findings:

It was found that correlation coefficients and RMS errors provide a valid indication of the dissimilarity between two ECG waveforms.

Significance to Biomedical Research and the Program of DCRT:

This project is applicable to the long term monitoring problem in intensive care units and directly supports the MIRU program.

Proposed Course of Project:

The software phase of this project will continue with the development of programs to investigate the frequency content of cardiac arrhythmias as a diagnostic factor. The addition of real-time data acquisition software is planned and will permit on-line acquisition and A/D conversion of electrocardiograms. Finally, analysis of electrocardiograms from remotely located patients will be performed utilizing a standard telephone transmission link or equivalent. Concurrently with the software development, the hardware digital arrhythmia analyzer will be tested, evaluated and modified, as appropriate, in order to optimize the accuracy and scope of the system.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.16
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Principles of Global Organization in Dense Volumetric Memories

Previous Serial Number: None

Principal Investigator: Harry Blum

Other Investigators: None

Man Years:

Total: .5
Professional: .5
Other: 0

Cooperating Units: None

Project Description:

Objectives:

To expand our conceptual base for understanding intellectual operation in animals and machines by providing a theoretical foundation for the parallel, pre-attentive, pre-logical operations.

Methods Employed:

Formalizing, developing, exploring and simulating models of parallel information processing in dense volumetric memory structures. These models use propagative pulse processes to facilitate a complete interchange of information widely distributed in memory. The project uses insights from widely diverse disciplines--mathematics, engineering, physiology, and psychology, etc.--to explore both structure and function in this ill-understood area.

Major Findings:

Formal physical models of such parallel processes have been previously defined. They have been extended this year to define rudimentary information structuring operations. A simple perceptual type "grammar" has been defined as a first step toward formalizing a method of imaging a world by small incremental perceptual operations that can be carried out by a parallel interactive processor. Relationships with perceptual processes and global brain function have been extended.

Significance to Biomedical Research and the Program of DCRT:

The work has broad potential in extending experimental directions in psychology and neurophysiology by proposing principles and constraints that may be operative in (1) the pre-attentive perceptual processes and (2) global brain processes. If relevant, the latter has important relationships with EEG and the non-specific projection processes such as are encountered in the recruiting and arousal phenomena of neuropsychology. In addition, the work is useful to DCRT and the general biomedical field, by proposing information retrieval structures which are geared to the imaging of a rich multi-dimensional cognitive, semantic and linguistic world. These structures have potential applicability to the study of such processes in higher animals and in developing software and hardware for accomplishing the functions with mechanism.

Proposed Course of Project:

1. To develop formal methods and bases for parallel intuitive processes.
2. To develop collaborative efforts in experimental psychology and neurophysiology within NIH and/or outside.
3. Simulate and explore, on digital computer, semantic structures and information retrieval problems occurring in a rich world.
4. To study the problem of new devices.

Honors and Awards: None

Publications:

Blum, Harry: "Global Brain Function: A Model Using Autonomous Broadcast Elements," Proceedings of Technical and Biological Problems of Control Symposium, Yerivan, Armenia, USSR Sept. 1968

Serial No. DCRT 4.17
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Data Compaction

Previous Serial Number: None

Principal Investigator: Paul Heffner

Other Investigators: None

Cooperation Units: None

Man Years:

Total: .1
Professional: .1
Other: 0

Project Description:

Objectives:

The objectives of the data compaction project are to reduce memory requirements when voluminous data require storage, and to enable data that would otherwise overload input/output channels to be transmitted and received through the channels.

Methods Employed:

Study has thus far centered around compression techniques that can be applied to continuously occurring analog data that is sampled periodically and stored for later reconstruction and processing. The techniques involved are those which could be implemented either with a computer, or, if appropriate, with external hardware.

Major Findings:

Two basic techniques were found which, for most analog signals, would allow implementation through straightforward software or hardware design. The first basic technique is that referred to as a zero order system extrapolation and reconstruction technique, and the second as a first order system extrapolation and reconstruction technique. The degree to which both of these techniques will provide storage reduction has been shown to depend upon the statistical nature of the data signal, the sampling rate, and the margin of error allowed by the experimenter in the reconstruction process. Algorithms for both techniques were generated.

Significance to Biomedical Research and the Program of DCRT:

One of the limiting factors facing on-line data acquisition systems is storage capacity for continuous high data volume experiments. Implementation of the above generated algorithms, either by software or by hardware, will allow continuous storage of data into one storage medium without causing data discontinuity. Some biological data requires fast sampling rates because it is very active and rapidly changing part of the time, even though it is inactive the rest of the time. If this data were to be captured and analyzed in a time-shared computer system, best use could be made of the system if the channel through which that data flows were allowed to be inactive when the data were inactive. A hardware data compressor, external to the computer, would allow for this type of system optimization.

Proposed Course of Project:

These techniques will be implemented for a specific application.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.18
1. Computer Systems Laboratory
2. Not applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: File Structure and Retrieval Processing System

Previous Serial Number: None

Principal Investigators: Scott I. Allen and William C. White

Other Investigators: John K. Knight and Thomas L. Tubbesing

Cooperating Units: None

Man Years:

Total: 1
Professional: 1
Other: 0

Project Description:

Objectives:

Most information storage and retrieval projects appear to have special requirements that preclude the use of an all-inclusive general purpose information processing language; however, the creation of a user-oriented set of well specified data processing routines can greatly simplify the programming tasks of file creation, and update data retrieval and report generation. The purpose of this project is the production and testing of such a package of routines to handle complex moderately large research data bases with a minimum of programming effort.

Methods Employed:

Preliminary experience at DCRT suggests that the programming language Pl/1 offers a sophisticated new tool which is relatively easy to learn and use for non-numeric computational data processing. This project uses PL/1 as the primary programming language to construct subroutines and macro instructions to be included in a user's program tailored to his specific needs.

The software capabilities include brief standard job control language sets, sort/merge commands for the organization of retrieval data, a PL/1 callable sort/merge subroutine, convenient plotter and line printer graph producing capabilities, powerful table-making features and a date conversion routine.

Major Findings:

Preliminary tests on a small synthetic data base have shown that the concept and implementation of a PL/1 language set of sub-routines and macros is a workable system for information retrieval problems. The system is being tested on an actual medical information system for approximately 150 patients.

Significance to Biomedical Research and the Program of DCRT:

This system of file structure and retrieval processing programs should be useful for many medical research data files. It will enable the DCRT programmers to construct data storage and retrieval programs with a minimum of effort.

Proposed Course of Project:

After extensive testing of the system, it is planned to make a program description manual available for users. This project should be completed in the present fiscal year.

Honors and Awards: None

Publications: None

Serial No. DCRT - 4.19
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Information Retrieval and Natural Language Data Processing

Previous Serial Number: None

Principal Investigator: Milos Pacak

Other Investigators: George Dunham, Helen DeFrancesco, Martin Epstein

Cooperating Units: None

Man Years:

Total: 3.5
Professional: 3.5
Other: 0

Project Description:

Objectives:

The goal is the development of a system for meaningful and timely retrieval of medical data for use by the scientific community.

a. Evaluation and implementation of modern automated data handling techniques and methods of linguistic analysis in order to handle narrative medical text in the pursuit of the overall goal.

b. The development of new techniques for programming, linguistic analysis and retrieval which are responsive to the user, that is, the medical community.

In the first stage, the research was limited to the early work in a manageable medical specialty, which represents a cross section of data handling and retrieval problems in the field of medicine.

Methods Employed:

The natural language data (NLD) processing system is represented by the 3-tuple

$$NLD = (T, D, G)$$

where T is the input text (pathology reports), D denotes the dictionary (SNOP) and G denotes context-sensitive grammar.

Grammatical analysis is performed on 3 levels:

a. Morphological analysis which implies the identification of productive terminal morphemes as markers of part-of-speech classes, and the set of transformation rules by which canonical forms are derived from adjectives and nouns. Nouns or their substitutes constitute the key semantic elements in the system and must often be derived from adjectives or other nominals.

b. Syntactic analysis implies the recognition of pseudo-sentence (utterances) boundaries, and the recognition of boundaries of noun phrases which constitute the conceptual units in the information retrieval system.

c. Semantic analysis is focused on the establishment of semantic correlations among the elements belonging to one of four major semantic categories as they are listed in the SNOP dictionary.

Computer implementation of morphological analysis is well underway. Study of the currently available programming languages and techniques for use in the project is a continuing effort.

Early and continual involvement of the user insures responsiveness of the system and allows for the evaluation of its effectiveness and acceptability. The retrieval needs of the scientific community are being carefully examined.

Major Findings:

1. The medical subfield of Pathology has been representative of problems across the field of medicine. A well-constructed dictionary of pathological terms, SNOP, was already in existence and has provided an excellent semantic and conceptual dictionary for the implementation of our techniques.

2. Medical text proved to be very useful for linguistic analysis.

3. The interest and support of the user has been stimulated, and it is anticipated that the system will represent a major contribution to the medical community.

Significance to Biomedical Research and the Program of DCRT:

The majority of medical data are recorded in natural language form (English language). In any linguistic analysis, it is necessary to assume that words convey certain meaning and that their meaning is determinable. The relation between a word and its meaning is the semantic correlation which is established by agreement and which, by acceptance, becomes convention. It is recognized today that computational linguistics is not only useful but necessary in any field in which the computer is called to interpret or analyze natural language, that is, indexing and classifying documents, indexing or abstracting pertinent documents, preparing computer-oriented microglossaries, analyzing the language of speakers with mental disorders, etc. The analysis and retrieval of medical data recorded in natural English by a computer requires the implementation of sophisticated techniques for natural language data processing.

Proposed Course:

Continuous refinement of the program with the main emphasis on the semantic analysis.

Honors and Awards: None

Publications:

Pacak, Milos: "Computational Morphology" in Austin, W. (Ed): Papers in Linguistics in Honor of Leon Dostert, Mouton Co., The Hague, 1967, pp. 134-145.

Pacak, Milos: "Homographs: Classification and Identification" in Etudes de Linguistique Applique (Studies in Applied Linguistics), Didier, Paris, pp. 89-105, 1968.

Serial No. DCRT - 4.20
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Experimental Medical Telecommunications

Previous Serial Number: None

Principal Investigator: Scott I. Allen, M.D.

Other Investigators: Michael Otten, Eric Swarthe, William White

Cooperating Units: None

Man Years:

Total:	1.3
Professional:	1.3
Other:	0

Project Description:

Objectives:

This project is concerned with the design, implementation, and field testing of new computer concepts and technology, as applied to medical information communication. It is oriented toward the goal of the continuing education of health professionals by providing rapid access to critical facts and calculations needed in patient-care decision-making by means of simple telephone communication facilities. The basic purpose of the project is to provide a method of giving the practicing physician and professional associates low-cost, easy-to-use, fast access to current medical information, computational assistance in the therapy protocols, and diagnostic assistance by computer programs used on a shared basis.

Methods Employed:

The basic terminal device being investigated in this project is the standard telephone available in every doctor's office. The lowest cost service can be supplied using a standard or Touch-tone telephone for the input of requests in digital codes, and the same telephone to receive an audio computer-generated output response. Other low-cost hard copy output devices are being investigated. Prototype programs have been written which include pediatric burn treatment calculation, intravenous drug compatibility information, disease-symptom complex listings for diagnostic assistance and a computer-aided instruction example of inter-active teaching dialogues. Computer service is supplied by commercial time-sharing systems, and is the most economical method of demonstrating the feasibility of the project. A Transmission Control Computer to handle line-switching, message buffering, code translating, and analog conversion is planned as the link between the telephone equipment in the doctor's office and the large, time-shared computers.

Major Findings:

Problems have been identified and solved in regard to the compatibility, reliability and availability of telephone communication equipment. Actual demonstrations have shown the project concepts to be economically feasible and have excited considerable interest in the project from medical administrators.

Significance to Biomedical Research and the Program of DCRT:

The technology being developed can be used to make research information readily available to the research scientist and medical practitioners. The ease of use, low-cost and ready acceptability of telephone input and audio response are receiving consideration in future plans for the main computational facility at NIH as provided by DCRT. The programming techniques and technical requirements for time-sharing, message switching and analog signal processing for communication by voice grade telephone lines can be of use in future expansion of the system facilities of DCRT and other university medical centers.

Proposed Course of Project:

The proposed course of this project envisages collaboration between NIH and selected university medical centers in various forms. Activities such as data base construction and maintenance, program specification and implementation, medical office field tests, service evaluations and equipment engineering could be sponsored by university medical centers in collaboration with DCRT. Prototype computer systems and devices would be tested and evaluated at DCRT and medical centers. Recommendations and specifications for the implementation of biomedical information networks would be prepared.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.21
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Analysis of Laboratory Spectral Data

Previous Serial Number: None

Principal Investigator: Marvin Shapiro

Other Investigators: Marie Chang, Carl Merril, H. Todd Miles

Cooperating Units: Laboratory of Neurochemistry, NIMH; Laboratory of Molecular Biology, NIAMD

Man Years:

Total: 1
Professional: 1
Other: 0

Project Description:

Objectives:

Mathematical curve fitting and pattern recognition methods are being implemented on the computer to recognize data patterns and to fit theoretical functions to the data.

Major Findings:

Programs have been written for analyzing ultraviolet (UV) and infrared (IR) spectra of oligonucleotides and the deconvoluting a series of overlapping data peaks.

Significance to Biomedical Research and the Program of DCRT:

The computer programs described should eventually have wide applicability at NIH, both by the many laboratories employing the same instruments for which the present programs were written, and by laboratories with other similar types of data which needs deconvoluting.

Proposed Course of Project:

The programs are in a preliminary stage of development. Work is being done in the areas of improving the methods of numerical analysis and curve fitting, and in setting up files of standardized data to be used for matching and curve-fitting. Eventually, many of the techniques and programs being developed will be used with on-line application, such as in NIAMD, Building 2.

Honors and Awards: None

Publications: None

Serial No. DCRT 4.22
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Bone Mineral Mass Measurement in-vivo

Previous Serial Number: None

Principal Investigator: William C. White

Other Investigators: William Vincent

Cooperating Units: Clinical Endocrinology Branch, NHI

Man Years:

Total: .25
Professional: .25
Other: 0

Project Description:

Objectives:

The purpose of the clinical study pursued by Dr. Ronald G. Evens of the Heart Institute is the detection of diseases which are characterized by a loss of mineral content of the bone. Quantitation of mineral loss has been a difficult clinical problem. A method of measurement of bone density using a mono-energetic gamma ray source to measure the absorption of the bone in-vivo has been developed. The calculations required to determine the integral of the absorption over the bone area studied are fundamentally simple, but variations in the measured data necessitates some smoothing techniques.

Methods Employed:

The data from the bone density measurements were recorded on punched paper tape, which was converted to punched cards, for input to a computer program written in FORTRAN and run on the 360/50. Reliability of the calculations and reproducibility of the measurements were checked by use of standard samples and multiple measurements.

Major Findings:

The bone density measurement method with computer analysis of the data has been shown to be a reproducible estimation of bone mineral content and useful for diagnosis and quantification of bone changes.

Significance to Biomedical Research and the Program of DCRT:

The calculations used in this FORTRAN program are simple and direct, and do not involve any new mathematical techniques. The program can be useful in other photon absorption problems.

Proposed Course of Project:

The project is being continued on a routine service basis.

Honors and Awards: None

Publications: None

Serial No. DCRT - 4.23
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Remote and Satellite Computation for National Institute of Mental Health Building 10 Scientists

Previous Serial Number: None

Principal Investigator: Daniel Syed

Other Investigators: William Holsinger and Martin Miller

Cooperating Units: None

Man Years:

Total:	3.5
Professional:	3.5
Other:	0

Project Description:

Objectives:

This project is intended to provide both on-line real-time and off-line computational support for research programs of National Institute of Mental Health Scientists currently scheduled to remain in Building 10. Specifically, on-line real-time data acquisition and computation is proposed in support of experiments in Problem Solving, Learning, Sleep and Dreaming, and Perception, and also in support of experiments relating the analysis of electroencephalographs and physiological variables to clinical diagnosis and classification of NIMH patients. Off-line computation is proposed in support of studies involving voluminous statistical processing as in the analysis of data from various surveys.

Methods Employed:

The on-line real-time requirements of Building 10 NIMH scientists were studied, and a local computer system specified. A similar analysis of off-line requirements led to the specification of a remote terminal to be located within NIMH Building 10 facilities.

Major Findings: None

Significance to Biomedical Research and the Program of DCRT:

Consistent with the development of time-sharing software on the Central Computer Facility IBM 360/50, the system will provide a basis for analysis and development of satellite computing techniques in a biomedical environment characterized by the presence of both high volume off-line data processing requirements and sophisticated on-line real-time requirements.

Proposed Course of Project:

Upon receipt of program approval, the satellite computing system will be procured on open bid. System software will be generated for this system. A remote terminal consisting basically of a small IBM 360/20 and associated printer and card equipment will be installed at NIMH in the next six months. This remote facility will operate in a queued batch process mode, and will utilize DCRT developed software that is presently being tested out.

Honors and Awards: None

Publications: None

Serial No. DCRT - 4.24
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Gerontology Research Center Computing System

Previous Serial Number: None

Principal Investigator: Daniel Syed

Other Investigator: Isaac Hantman

Cooperating Units: None

Man Years:

Total:	2
Professional:	2
Other:	0

Project Description:

Objectives:

This project is intended to provide support for research programs of the Gerontology Research Center in the areas of on-line computation and control, analog to digital conversion and off-line data processing. The on-line computation capability is designed to support experiments in Problem Solving while the on-line control capability is to be utilized in the control of blood glucose/insulin infusion rates. The analog to digital conversion and off-line computation capabilities will be used in the analysis of electrocardiograms, physiological data, scintillation counter data and nuclear magnetic resonance data, etc.

Methods Employed:

The data processing requirements of the Gerontology Research Center have been analyzed in depth, and a system is being specified through utilization of standard engineering techniques.

Major Findings: None

Significance to Biomedical Research and the Program of DCRT:

None

Proposed Course:

The computer system, once specified, will be procured on open bid. Limited system software generation will be necessary to provide for efficient use of the computer system.

Honors and Awards: None

Publications: None

Serial No. DCRT - 4.25
1. Computer Systems Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Computer System for the Laboratory of Psychology, Section on Comparative Behavior, Poolesville

Previous Serial Number: None

Principal Investigator: Daniel Syed

Other Investigators: Martin Miller, Kenneth Kempner

Cooperating Units: None

Man Years:

Total: .1
Professional: .1
Other: 0

Project Description:

Objectives:

This project is designed to provide a real-time data acquisition computer system in support of on-line experiments being conducted by the Section on Comparative Behavior, Laboratory of Psychology, NIMH. Such a system is to provide control of sophisticated experimental equipment and also to permit extended periods of operation to be accomplished without operator intervention. Limited off-line computational capacity will be provided to meet requirements for statistical analysis.

Methods Employed:

A detailed study of the computational and control requirements of the Section on Comparative Behavior, NIMH, was performed, and standard engineering techniques are being used, in the design of a small computer system.

Major Findings: None

Significance to Biomedical Research and the Program of DCRT:

None

Proposed Course of Project:

The computer system will be procured on open bid.

Honors and Awards: None

Publications: None

July 1, 1967, through June 30, 1968

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities	1. DCRT - 5
2. PHYSICAL SCIENCES LABORATORY	3. Dr. G. H. Weiss

I. SUMMARY

During the present reporting period, the Physical Sciences Laboratory grew from two professionals to ten. In consequence ,not only has work gone forward at an accelerated pace on projects already started,but many new areas of investigations have been opened. These include the theoretical calculation of conformation of biologically interesting molecules, the development of statistical mechanical models of membrane transport phenomena, developments in the theory of nuclear magnetic resonance experiments, and the application of nonlinear numerical techniques for the resolution of data from biochemical separation experiments.

II. CURRENT BRANCH PROGRAMS

A. Objectives

To develop a group with theoretical interests to analyze biological phenomena in the terminology of theoretical physics and theoretical chemistry. To act as consultants in theoretical aspects of physics and chemistry to experimental scientists at NIH and to members of DCRT who may require such services in conjunction with their own work.

B. Progress of Current Programs

1. Development of Ultracentrifugation Theory

a. The program for generating accurate solutions to the Lamm equation which had been running on the 360/75 in New York has been transferred to the 360/75 in Greenbelt. Modifications have been made in it so that it now runs approximately twice as fast as in New York.

b. An extensive development of the theory and of relevant numerical solutions of the Lamm equation has been made for band centrifugation.

c. A theory has been developed for centrifugation in a density gradient, and relevant numerical solutions are being generated.

2. Theory of the Helix-Coil Transition in Polypeptides

a. Recent experimental developments indicate that the currently accepted theories of the helix-coil transition are incorrect, and do not describe the phenomenon even qualitatively. Further experiments on this phenomenon are being carried out, and a theory consistent with known experimental facts is being developed.

3. Computer Processing of NMR Data

a. Numerical procedures and programs have been developed for the interpretation of NMR data, particularly for the resolution of spectra. These programs are presently being used by members of NIAMD.

4. Molecular Model Building

a. Analysis of small molecules has been carried out, particularly on formic and acetic acids, and on the base-pairing problem, using potential functions developed during the last year. Excellent agreement has been obtained between present calculations and thermodynamic and crystallographic data.

5. Biophysical Analysis

a. A model has been developed for the effects of noise on nerves described by equations similar to those of Hodgkin and Huxley. This model predicts the shape of threshold firing curves as a function of the noise, as a function of bathing solutions, and certain drugs. Good correlation has been obtained between results of the theory and experimental results.

6. Excitation and Transport Properties of Fluids

a. A theoretical description of certain microscopic properties has been developed, and good agreement obtained with computer studies of the same problems at other laboratories.

7. Theory of Cell Membranes

a. The theory of electrostatics has been used to study the feasibility of suggested mechanisms for transport across membranes. It has been shown that ionic interaction with the low dielectric membrane is an important barrier to flow. However, it can be lowered considerably by highly polarizable material at points in the membrane.

8. Consulting Services

a. The analysis of experiments on the effects of varying concentration and time exposure of several antileukemic drugs on tissue cultures of human leukemic cells has been completed. The technique is a useful one, and provides results in a laboratory setting consistent with certain clinical findings. Hence this type of experiment can be used for a study of other possible parameters in the use of antileukemic drugs.

b. Further investigations on nonlinear curve fitting techniques are being undertaken, in connection with the continuing input of biochemical data. In particular, Dr. James Ferretti is collaborating with several members of NIAMD in the preliminary specification of programs and options for a computer to be used exclusively for processing data from the laboratories in Building 2.

9. Fundamental Studies

a. A theory of the kinetics of red cells in transient conditions such as after acute hemolysis, has been developed. The theory is consistent with known experimental facts and will be useful for the interpretation of labelling experiments after it is further checked out.

b. Accurate calculations of the diffusion constant of rod-like polymer molecules have been made. It has been shown that the commonly accepted Kirkwood-Riseman theory leads to spurious results in the region of physical interest.

c. The stochastic theory of the kinetics of chemical reactions has been shown to lead to the same result as the deterministic, or mass-action theory, in the thermodynamic limit.

d. Preliminary calculations have been made for nuclear magnetic resonance in the presence of two radio frequency fields.

e. It has been shown that over 100 leads are required for an accurate measurement of the equivalent heart dipole.

C. Program Plans

1. Development of Ultracentrifugation Theory

Work will be begun on numerical solution of the Lamm equation for associating systems, and for density gradient centrifugation. Hopefully, work will be completed on the analysis of centrifugation in the presence of large pressure gradients.

2. Molecular Model Building

Theoretical conformations will be calculated for crystals and a start will be made on similar calculations for several protein molecules.

3. Biophysical Analysis

The work done to date suggests that a more general theory of noise in nonlinear systems is required for the understanding of much interesting nerve behavior. Hence similar studies will be undertaken on other model systems.

4. Theory of Cell Membranes

Calculations will be undertaken to ascertain the effects of electrostriction and carrier molecules on membrane transport.

Serial No. 5.1
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 20, 1968

Project Title: Theory of the Ultracentrifuge

Previous Serial Number: 5.1

Principal Investigator: George H. Weiss, Ph.D.

Other Investigators: Ralph Nossal, Ph.D., Richard I. Shrager, David Yphantis, Ph.D.

Cooperating Units: Charles W. Boone, M.D., NCI

Man Years

Total:	.70
Professional:	.50
Other:	.20

Project Description:

Objectives:

To determine the effects of various factors such as concentration dependent sedimentation, pressure, density gradients, variations in rotor speed, and polydispersity on current techniques for determining molecular weights. To devise corrections and new techniques of ultracentrifugation which bypass or eliminate these effects.

Methods:

The methods employed include numerical solutions to partial differential equations and classical analysis.

Major Findings:

Formulae have been developed for the time to equilibrium in density gradient centrifugation. Preliminary calculation of optimal density gradients and other relevant parameters to separate tumor cells in a Ficoll gradient have been successful. The theory of band centrifugation in non-ideal solutions has been developed.

Significance to Biomedical Research

Density gradient centrifugation is one of the most significant modern tools for separating molecular species and for populations of macroscopic tumor cells. Band centrifugation is of considerable importance in the study of biologically interesting molecules since very little material is required for such experiments.

Honors and Awards: None

Publications:

Weiss, George H. (with I. Billick, M. Schulz): Quasi-equilibrium Experiments with Rotor Deceleration, Journal of Physical Chemistry, 71: 2496-2502, 1967.

Weiss, George H. (with M. Dishon, D. Yphantis): Numerical Solutions to the Lamm Equation III. Velocity Centrifugation, Biopolymers, 5: 691-713, 1967.

Weiss, George H. (with I. Billick, M. Dishon, D. Yphantis): Numerical Solutions to the Lamm Equation IV; Rotor Slowing Experiments, Biopolymers 5: 1021-1028, 1968.

Weiss, George H. (with M. Dishon, D. Yphantis): Numerical Solutions to the Lamm Equation V: Band Centrifugation, Proceedings of the New York Academy of Sciences Conference on Ultracentrifugal Analysis (to appear).

Serial No. 5.2
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Theory of the Helix-Coil Transformation in Polypeptides in Solution

Previous Serial No.: None

Principal Investigator: James A. Ferretti, Ph.D.

Other Investigators: Livio Paolillo, Ph.D. (NIAMD)

Cooperating Units: NHI, NIAMD

Man Years:

Total:	.45
Professional:	.40
Other:	.05

Project Description:

Objectives:

To determine the effects of various factors such as Van der Waals interactions, hydrogen bonding, and electrostatic effects on the stability of helical polypeptides. To formulate models for the helix-coil transformation by the application of statistical thermodynamics.

Methods:

Applying NMR spectroscopy as the experimental approach towards evaluating the relative importance of the various interactions and then comparing the theoretical calculations with experimental data.

Major Findings:

It is possible to quantitatively determine the helix-coil concentration ratio under various experimental conditions and to completely follow the helix-coil transformation in various polypeptides. These results clearly showed that previous models do not adequately describe the phenomenon.

Significance to Biomedical Research

Polypeptides serve as protein model compounds and knowledge of the helix-coil transformation is essential to a complete understanding of the phenomenon of protein denaturation.

Honors and Awards: None

Publications:

Ferretti, James, A.: 100 Mc./sec Nuclear Magnetic Resonance Study of the Helix-coil Transformation in Polypeptides, Chemical Communications, 1030 (1967).

Serial No. 5.3
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Computer Processing of Nuclear Magnetic Resonance (NMR) Spectral Data

Previous Serial Number: None

Principal Investigator: James A. Ferretti, Ph.D.

Other Investigators: Mildred McNeel

Cooperating Units: None

Man Years

Total:	.45
Professional:	.40
Other:	.05

Project Description:

Objectives:

To develop methods, using the quantum mechanical NMR spin Hamiltonian, to analyze complex NMR spectra. To devise methods for computer simulation of experimental spectra and to decompose experimental spectra into their individual component frequencies and intensities.

Methods:

Iterative computer techniques are employed to approximate experimental NMR spectra by least squares fits.

Major Findings:

It is possible to completely analyze complex NMR spectra with the use of a computer. These results provide means for testing the sensitivity of the experimental spectrum changes in the various parameters.

Significance to Biomedical Research:

NMR spectra provide fundamental information about the structure and conformations of biologically interesting molecules.

Honors and Awards: None

Publications:

Ferretti, James A. (with E. Lustig, E. P. Ragelis, and N. Ivy), The Analysis of AA'BB' Nuclear Magnetic Resonance Spectra by Weak Double Irradiation. Application to Two Isomeric Cyclobutane Derivatives. Journal of the American Chemical Society 89, 3953 (1967).

Serial No. 5.4
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Molecular Model Building Using Theoretically and Empirically Determined Intra- and Intermolecular Potential Functions

Previous Serial Number: 3.14

Principal Investigator: William P. Minicozzi, M.D.

Other Investigators: Dan Bradley, Ph.D. (NIMH), James Kiefer, Ivan Darvey, Ph.D. Virginia Aandahl, Howard Nash, M.D. (NIMH).

Cooperating Units: Laboratory of Neurochemistry, Section on Physical Chemistry, NIMH

Man Years:

Total:	1.0
Professional:	1.0
Other:	0.0

Project Description:

Objectives:

Elucidation of the nature of protein folding.

Methods Employed:

X-ray crystallographic and electron scattering data are used to determine bond lengths and fixed bond angles for the molecular system under consideration. Then a linear combination of atomic orbitals is used to calculate charge distributions in the molecule under consideration among the various atoms consistent with the experimentally determined dipole moment of the molecule. An atom-atom interaction energy is the sum of four components in our model:

1. Electronic repulsion due to overlap of orbitals.
2. Electron correlation energy arising from the induced instantaneous dipoles.
3. Electrostatic energy, calculated by making a monopole-monopole approximation. Values of atomic monopoles are obtained as described above.

4. Static induced dipole energies calculated from an approximate formulation, which becomes more exact as the internuclear distance increases. Using quantum mechanical and classical mechanical derivations for functions and empirically determined values for some of the derived parameters, atom-atom potential functions are constructed. We then use these potential functions to calculate atom-atom interaction energies as a function of interatomic distance. Finally, the molecular system under consideration is allowed to undergo all possible internal rotations and assume a variety of intermolecular configurations. The energy of each is calculated by summing overall atom-atom interactions. In many instances, the accuracy of these procedures may be checked by comparing calculated results with experimentally determined energies and configurations.

The calculations necessary for these procedures require the development and testing of linked computer programs.

We are in the early stages of displaying molecules on an oscilloscopic screen. This will be an important part of the total procedure.

Major Findings:

Approximate intermolecular potential functions can be used quite effectively to predict the energies and conformations of simple molecular systems. They have not yet been tried on large molecular systems (e.g. proteins).

Significance to Biomedical Research:

Accurate prediction of the energies of molecular configurations enable one to know whether specific chemical reactions will or will not occur and why. This information should be of considerable importance to chemotherapy.

Honors and Awards: None

Publications: None

Serial No. 5.5
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Biophysical Analysis

Previous Serial Number: None

Principal Investigator: Ralph J. Nossal, Ph.D.

Other Investigators: None

Cooperating Units: Harold Lecar, Ph.D., Biophysics Laboratory, NINDB.

Man Years:

Total:	.40
Professional:	.35
Other:	.05

Project Description:

Objectives:

To relate the fluctuations in firing thresholds of nerves to the chemical and physical processes underlying excitation. To analyze existing data, in order to test theories concerning mechanisms of transport of ions across nerve membranes.

Methods:

Existing neurophysiological equations (the Hodgkin-Huxley equations) have been modified to include fluctuating forces. Methods of non-linear mechanics and statistical physics have been applied to analyze the equations.

Major Findings:

It has been possible to relate the functional shape of the threshold firing curve, and the width of the threshold region, to models of thermal noise and conductivity fluctuations. There is also good correlation between the theory and results of certain experiments in which temperature, bathing solutions, and drugs have been used to change the threshold properties of nerve axons.

Significance to Biomedical Research:

It is hoped that the study will facilitate better understanding of the physical processes underlying the excitation and propagation of nervous impulse.

Publications: None

Serial No. 5.6
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Physico-chemical Properties of Macrocyclic Antibiotics

Previous Serial Number: None

Principal Investigator: Ralph J. Nossal, Ph.D.

Other Investigators: James A. Ferretti, Ph.D.

Cooperating Units: Gerald Ehrenstein, Ph.D., Biophysics Laboratory, NINDB

Man Years:

Total:	.25
Professional:	.25
Other:	.00

Project Description:

Objectives:

Various macrocyclic antibiotics (e.g. Gramicidin, Valinomycin, Nonactin) facilitate transport of monovalent cations across biological structures such as mitochondrial and plasma membranes. This project is directed towards understanding the molecular mechanisms underlying facilitated transport and, in particular, the ion selective aspects of the latter.

Methods:

Physical probes such as analytic ultracentrifugation, high resolution NMR, and laser light scattering are being applied to determine the molecular structure and properties of these antibiotics. When necessary, existing physical theory is extended in order to support suitable modifications of experimental technique. Reconstituted phospholipid bilayers are used in conjunction with these studies, and new experimental procedures are developed when appropriate.

Major Findings:

The project has only recently been undertaken; no major results have yet been obtained.

Significance to Biomedical Research:

It is hoped that these studies will lead to better understanding of the details of the pharmacological action of macrocyclic antibiotics. Further, the latter may be analogs of cation transport "channels" in excitable tissues, and it is of some interest to establish their relevancy in this regard.

Publications: None

Serial No. 5.7
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Excitation and Transport Properties of Fluids

Previous Serial Number: 5.4

Principal Investigator: Ralph J. Nossal, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.45
Professional:	.40
Other:	.05

Project Description:

Objectives:

To provide basic knowledge concerning the excitation properties and transport properties of fluids,to provide theoretical explanations of experimental evidence of high frequency collective atomic motions of simple classical fluids.

Methods:

Theoretical techniques of mathematical physics and statistical mechanics are employed, in order to develop new physical theories.

Major Findings:

A theoretical description of the properties of fluids has been developed and its consequences are being explored. Preliminary analysis indicates good agreement with results of neutron scattering experiments on simple fluids.

Significance to Biomedical Research:

Almost all biological phenomena occur in a fluid environment. A number of fundamental questions concerning the physical behavior of fluids yet remain unanswered. Their elucidation will ultimately facilitate better understanding of the functions and properties of biological systems.

Publications:

Nossal, R. (with R. Zwanzig), Approximate Eigenfunctions of the Liouville Operator in Classical Many-Body Systems. II. Hydrodynamic Variables, Physical Review 157, 120 (1967).

Nossal, R.: Collective Motion in Simple Classical Fluids, Physical Review 166, 81 (1968).

Nossal, R.: Hamilton's Principle for Continuum Viscoelestic Fluids, J. Mathematical Physics (to appear).

Serial No. 5.8
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Intermolecular Forces Acting in the Cell Membrane

Previous Serial No.: None

Principal Investigator: V. Adrian Parsegian, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.55
Professional:	.5
Other:	.05

Project Description:

Objectives:

To identify and calculate those intermolecular forces important in stabilizing the cell membrane and in determining transport of materials across the cell boundary. So far these have been coulombic interactions between charged species, short-range interactions of the van der Waals type, and charge interactions with media of different shapes and dielectric properties.

Methods:

Classical and quantum-mechanical treatment of electromagnetic and statistical-mechanical behavior as well as molecular models of specific molecular associations

Major Findings:

Van der Waals forces act as an interfacial tension between lipid aggregates and aqueous medium. Ionic interaction with the low dielectric membrane is an important barrier to ion flow; it can be lowered by the presence of highly polarizable material at points in the membrane.

Significance to Biomedical Research:

The transport of ionic and neutral species across the cell membrane is strongly dependent on interaction with the membrane material as well as on the structure of that material.

Honors and Awards: None

Publications:

Parsegian, V. A.: An Energetic Model of Ionic Lipids in the Liquid-Crystal State, Proceedings of the International Conference on Biological Membranes, Frascati, Italy (to appear).

Serial No. 5.9
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 20, 1968

Project Title: Consulting Services

Previous Serial Number: 5.3

Principal Investigators: George H. Weiss, Ph.D., Richard I. Shrager

Other Investigators: Mildred McNeel, Yashar Hirshaut, M.D., Todd Miles, Ph.D., Frank Howard, Ph.D., Donald Young, M.D.

Cooperating Units: Medicine Branch, NCI, Laboratory of Molecular Biology, NIAMD, Clinical Center

Man Years:

Total:	1.1
Professional:	1.0
Other	.1

Project Description:

To provide consulting services in biometry, applied mathematics, theoretical physics and chemistry to workers who are primarily in experimental fields.

Methods:

The methods include statistical analysis, theoretical physics and chemistry, and applied mathematics.

Major Findings:

The use of human leukemic cells in culture has been shown to be useful in describing the effects of antileukemic drugs *in vivo*. Experiments indicating the effects of varying concentration and time of contact of drugs with these cells indicate that tissue cultures can be used as an assay device, and to suggest new drug regimes in leukemia.

Numerical techniques have been devised to correlate data from circular dichroism and from optical rotatory dispersion experiments, and to decompose them into spectral components.

Methods:

Standard statistical techniques have been used for the first project. Methods for nonlinear curve fitting and for the evaluation of Kramers-Kronig relations have been devised for the second project.

Honors and Awards: None

Publications: None

Serial No. 5.10
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Fundamental Studies

Previous Serial Number: 5.4

Principal Investigators: George H. Weiss, Ph.D., James A. Ferretti, Ph.D., Ralph Nossal, Ph.D., Gershom Zajicek, M.D.

Other Investigators: Livio Paolillo, Ph.D., Irwin Oppenheim, Ph.D. and Robert Zwanzig, Ph.D.

Man Years:

Total:	4.15
Professional:	3.7
Other:	.45

Project Description:

This project encompasses several lines of investigation, some, but not all of which relate to biomedical problems. These include theoretical studies of red cell kinetics, the calculation of diffusion properties of long chain polymers, the comparison between deterministic and stochastic theories of chemical reactions, development of the theory of nuclear magnetic resonance, design studies for a new electrocardiograph, and basic studies in statistical mechanics.

Major Findings:

A theory has been developed for red cell kinetics after acute hemolysis. The theory is phrased in terms of measureable parameters like red cell volume and osmotic fragility, and is in accord with presently known facts about red cell kinetics. Further experiments are needed to develop some of the necessary parameters of the model.

It has been shown that the classical calculation of the diffusional properties of rod polymers is incorrect, and that a more accurate account of boundary conditions is required in the hydro-dynamic theory.

For some time it has been conjectured that the stochastic theory of chemical kinetics would predict the existence of macroscopic fluctuations not due to experimental error. This has now been settled, as it has been shown that the fluctuations from results predicted by the deterministic theory are negligible.

A density matrix formulation for NMR relaxation in the presence of a second radio frequency field has been shown to be feasible.

Calculations of the number of leads required for accurate determination of the equivalent heart dipole indicate that a number of the order of 150 is necessary to achieve errors of less than 15%.

Models have been developed for the decay of correlations in simple mechanical systems with large numbers of degrees of freedom. It has been shown that the introduction of coupling does not change any of the qualitative results of the theory developed for independent particles.

Methods:

The methods used include partial differential equations, statistical theory, classical analysis, numerical analysis, and other techniques commonly used in theoretical physics.

Significance to Biomedical Research:

The work in red cell kinetics may lead to new interpretations of labelling experiments. The work in polymer diffusion is constantly used in the interpretation of experiments on DNA. A clear delineation of the region of validity of the theory will be of use in the interpretation of discrepancies between experiments and theory. The work on the electrocardiograph may lead to one which will be more useful for pediatric cardiology.

Awards and Honors: None

Publications:

Ferretti, James A. (with L. Paolillo): The Signs of Geminal and Directly Bonded Hydrogen-Phosporus Coupling Constants. Ricerca Scientifica CCSS-11, 103-105, 1967.

Weiss, George H. (with H. Pettigrew): Epidemics with Carriers, The Large Population Approximation. J. Appl. Prob. 4, No. 2, 257-286, 1967.

Weiss, George H. (with J. Gart): Graphically Oriented Tests for Host Variability in Dilution Experiments. Biometrics 23, 269-284, 1967.

Weiss, George H. (with I. Oppenheim and K. Shuler): On the Decay of Initial Correlations in Stochastic Processes. J. Chem. Phys. 46, 4100-4114, 1967.

Weiss, George H. (with I. Billick and M. Schulz): Quasi-equilibrium Experiments with Rotor Deceleration. *J. Phys. Chem*. 71, 2496-2502, 1967.

Weiss, George H.: On the Master Equation Formulation of Chromatography Theory. *Separation Science* 2, 551-554, 1967.

Weiss, G. H.: An Introduction to Lattice Dynamics. In *Many-Particle* Physics. ed. by E. Meeron (Gordon & Breech, 1967) 129-182.

Weiss, G. H.: *First Passage Time Problems in Chemical Physics* in *Advances in Chemical Physics* XIII. (Wiley & Sons, New York) 1-18, 1967.

Weiss, George H.: (with I. Oppenheim and K. E. Shuler): Stochastic Theory of Multistate Relaxation Processes. *Adv. in Molecular Relaxation Proc*. 1, 13-68, 1967

Weiss, George H. (with R. Hoye, J. Gart, Ketcham, G.) Potentiation of Laser Oncolysis with Pretreatment X-irradiation. *Rad. Res*. 32, 112-117, 1967.

Weiss, George H.: The Intersection Delay Problem with Gap Acceptance Function Depending on Space and Time. *Trans. Res*. 1, 367-371, (1967).

Weiss, George H. (with Dishon, M. and Yphantis, D. A.) Numerical Solutions to the Lamm Equation III. Velocity Centrifugation. *Biopolymers* 5, 691-713, 1967.

Weiss, George H. (with Billick, I., Dishon, M., and Yphantis, D. A): Numerical Solution of the Lamm Equation IV; Rotor Slowing Experiments. *Biopolymers* 5, 1021-1028, 1967.

Weiss, George H. (with Nossal, R.): Analysis of a Generalized Ladenburg-Reiche Integral. *J. Quantit. Spect*. 8, 763-771, 1968.

Weiss, George H.: Equations for the Age Structure of a Growing Population, *Bull. Math. Biophys*. (to appear).

Weiss, George H.: An Introduction to the Statistical Theory of Irreversible Processes, In *Irreversible Thermodynamics* (to appear).

Weiss, George H. (with R. Zwanzig, J. Kiefer): On the Limits of Validity of the Kirkwood-Riseman Theory, *Proc. Nat. Acad. Sci*. (to appear).

Weiss, George H. (with Dishon, M. and Yphantis, D. A.) Numerical Solutions for the Lamm Equation. V. Band Centrifugation. *Proc. Conf. on Ultracentrifugal Analysis* (to appear).

Weiss, George H. (with Grover, N.): Theoretical Distribution of Two-Dimensional Projections in Electronmicroscopic Sections. *Proc. Nat. Acad. Sci*. (to appear).

Weiss, George H.: Some Models for the Decay of Initial Correlations in Dynamical Systems, *Adv. in Chem. Phys.* (to appear)

Zajicek, Gershom: A Computer Model Simulating the Behavior of Adult Red Blood Cells, *Journal of Theoretical Biology* (to appear)

July 1, 1967 through June 30, 1968

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT - 6
Serial Number

2. HEURISTICS LABORATORY

3. James R. Slagle
Chief

I. SUMMARY

This Laboratory which was activated during this reporting period is currently pursuing two broad objectives which are intended to apply the techniques from computer research to problems in biomedical research. The projects which embody these objectives are qualitatively described. The two projects include the development of programs for answering questions and the design and development of a computing system for the processing of biological images. Both of these projects are still in the initial stages of development.

II. CURRENT LABORATORY PROGRAMS

The Heuristics Laboratory which was activated half way through this reporting period has been formed from newly recruited personnel and the Biological Image Processing group which was transferred from the Computer Systems Laboratory. This Laboratory is presently composed of 12 scientific and 2 clerical individuals. The Laboratory will use as its main computing system the PDP-10 computer which was purchased during the reporting period.

A. Objectives

This Laboratory is currently pursuing two broad objectives:

1. To develop concepts, techniques and programs for the automatic answering of questions and the solving of problems.

2. To design and develop a computing system and the associated programming techniques for the on-line, interactive processing of biological images.

B. Progress

The objectives previously set forth represent the current broad goals of the Laboratory. Within each broad objective individuals have begun projects which realize relatively separable sub-goals. Greater detail is supplied in the individual project reports.

Progress Toward Objective #1 (To develop concepts, techniques and programs for the automatic answering of questions and the solving of problems.)

There are many problem areas within the biomedical environment in which facts emerge and deductive reasoning from the facts must be done. Various studies in the past have shown that the computer can be used to do deductive reasoning. Two serious difficulties prevent the application of computers to realistic problems. They are:

1. The formulation of a question has a very important influence on the answerability. A poor formulation can make a question effectively unanswerable.

2. As the number of facts in the data base increases, the time required for doing deductive reasoning increases beyond practical limits.

In order to overcome the first difficulty, studies in the formulation of questions and problems have begun. The outlook for these studies is a developing theory of question and problem types. As distinct types of questions and problems arise, computer programs are being written. Work towards solving the second difficulty has been concerned with developing strategies for determining the relationship of facts to one another and to the process of utilizing the facts. The intention is to use only relevant facts in the answering of a question and the solving of a problem. Greater detail is provided in Individual Project Report DCRT 6.1.

Progress Toward Objective #2 (To design and develop a computing system and the associated programming techniques for the on-line, interactive processing of biological images.)

Work has been completed on the negotiation of a contract with the Digital Equipment Corporation for the purchase of the Laboratory's PDP-10/50 computer-display system. The negotiations have been completed and the computer is scheduled for delivery in November 1968. The software required for providing an on-line, reactive system for biological image processing is being designed. It has been decided to use the list processing language LISP as the high level language for integrating and coordinating the various components of the system. When the system becomes operational, we expect that biologists and other scientists with image processing problems will use it in collaboration with computer specialists of this Division to develop specific, problem-oriented algorithms. Greater detail is provided in Individual Project Report DCRT 6.2.

General Remarks

The staffing of the projects in this Laboratory has been hindered by the difficulties in obtaining adequately experienced personnel. As the role of the Laboratory expands through the acquisition of the PDP-10 computer and the initiation of other projects, further recruiting will have to occur. While space for the computer has been found, the location of the space leaves much to be desired. The biological image processing computer facility should be spatially proximate to the research activities. The role of this computer is not a peripheral data processor but an integral part of the scientific process.

The space for the present staffing of this Laboratory is in part inadequate. As additional individuals are added to this Laboratory, it becomes imperative to find additional space. An effort should be made during the next reporting period to integrate the computing facility with an enlarged block of office space.

Serial No. DCRT - 6.1
1. Heuristics Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Automatic Question-Answering

Previous Serial Number: None

Principal Investigator: James R. Slagle, Ph.D.

Other Investigators: Chin-Liang Chang, Ph.D., John K. Dixon,
Richard J. Feldmann, Deena A. Koniver,
Richard C. T. Lee, Ph.D.

Cooperating Units: None

Man Years

Total:	5.1
Professional:	3.8
Other:	1.0

Project Description:

Objectives:

1. To develop concepts and formalisms for the representation of facts, questions and problems.

2. To develop strategies which reduce the amount of computation required to answer questions and solve problems.

Methods Employed:

As new concepts, formalisms and strategies arise, internal papers are generated. The computational feasibility of these proposals are studied and computer programs are written and debugged. Presently, the Q-32 computer in Santa Monica, California is being used. The computer language LISP which is a laboratory standard is also being utilized on the IBM 360/50 computer.

Major Findings:

A computer program written to test a new inference rule for facts in question-answering has shown that significantly fewer working facts are generated during the course of the answering of a question. Saturation of computer memory in the past has been one of the factors which prevented the development of a practical question-answering system. A hypothesis concerning the generation of models for the mechanization of inductive inference was tested by a computer program. The results indicated that too many instances of a model could occur. A reformalization and testing of the General Problem Solver concepts has indicated that certain problems which are effectively unanswerable with the inference rule type programs can be answered. The concepts used to decide effective courses of action in a multipurpose search program have been applied to the environment of question-answering by resolution.

Significance to Biomedical Research and the Program of DCRT:

Several demonstrations of a question-answering program written during this reporting period have been made to members of other groups in DCRT. A fully developed question-answering-problem solving program would allow the working scientist to turn over to the computer routine questions and problems. The computer would solve these routine matters while the scientist was attending to the more important and difficult problems.

Proposed Course of Project:

1. The development of new methods for question-answering will continue. Whenever possible, programs will be written to test these ideas.

2. A collaborative project with the Division of Research Facilities and Resources will most probably begin. In this project deductive question-answering techniques will be applied to pharmacological data embedded in qualitative models of human anatomy and physiology.

3. As the PDP-10 computer becomes available programs and activity will be transferred from the existing computer services.

Honors and Awards: None

Publications:

Slagle, James R.: Automatic Theorem Proving with Renamable and Semantic Resolution, Journal of the ACM, Vol. 14, 4, (Oct. 1967), 687-697.

Slagle, James R.: Generalizations of a Complex Analogue of the Real Tchebichev Polynomial Theorem, American Mathematical Monthly, Vol. 75, 1, (Jan. 1968), 58-59.

Slagle, James R. (with P. Bursky): Experiments with a Multipurpose, Theorem-Proving Heuristic Program, Journal of the ACM, Vol. 15, 1, (Jan. 1968), 85-99.

Chang, C. L.: Fuzzy Topological Spaces, to appear in Journal of Mathematical Analysis and Applications.

Serial No. DCRT 6.2
1. Heuristics Laboratory
2. Not Applicable
3. Bethesda

PHS - NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Biological Image Processing

Previous Serial Number: DCRT - 4.7

Principal Investigators: H.W.Vreenegoor, DCRT
Lewis E. Lipkin, M.D.,NINDB

Other Investigators: Malcolm C. Bruce, Sam Bryan,
Edward C. Hill, Louis Hodes,Ph.D.

Cooperating Units: Section on Pathology, PRB, NINDB

Man Years
Total: 6.3
Professional: 6
Other: 0.3

Project Description:

Objectives:

1. Development and utilization of new techniques and devices to permit the study of biological images in order to determine significant characteristics of these images for classification and identification purposes.

2. Research directed toward the development of a "natural language" communication system to optimize biologist-computer interactions in the context of image processing.

3. Study, evaluation, and implementation of techniques permitting semi-automatic and/or automatic processing of large volumes of biological images.

Methods Employed:

A number of computer programs were developed on the IBM 360 computer for transforming digitized picture data to picture data compatible with the Stromberg-Carlson 4020 microfilm printer.

A picture processing oriented language, called PAX, was developed under contract by the University of Maryland for the IBM 360 computer.

An on-line reactive approach, using LISP as the high level language, was studied to determine its feasibility and utility for picture processing. Members of this group have worked on the negotiation of a contract with the Digital Equipment Corporation for the purchase of a PDP-10/50 computer-display for use by the laboratory. The contract has been signed. The system is scheduled for delivery in November 1968.

Major Findings:

Experience with the Stromberg-Carlson 4020 has shown that "natural" looking biological pictures can be reproduced from digitized data. The process is most useful for producing occasional high quality prints or film. It is too cumbersome and costly for large numbers of pictures.

The PAX picture processing language has provided a capability for analyzing pictures in the batch processing mode. Its primary function will be the determination of the usefulness of newly developed picture processing algorithms.

Studies of the feasibility of using on-line, interactive LISP with PAX-like processes, show it to be an important step towards achieving a system for rapid on-line development of picture processing algorithms.

Significance to Biomedical Research and the Program of DCRT:

The project provides resources required for the study of biological images in an objective and repeatable manner. The interaction of the biologist with selected and displayed images should provide information important towards acquiring a better understanding of the underlying structure. The project applies state-of-the-art computing devices and techniques to an important segment of biological investigation.

Proposed Course of Project:

1. Development and implementation of a LISP based on-line reactive system for the PDP-10/50 with the following major characteristics:
    a. capability of creating and handling display lists using the modified DEC 340 display
    b. capability to handle PAX or PAX-like picture processing techniques
    c. capability to handle FORTRAN and assembly language generated programs
    d. capability to accept Rand Tablet data
2. Development of specific picture processing algorithms.

3. Study of the utility of a flexible, programmable flying spot scanner for the project.

Honors and Awards: None

Publications: None

DIVISION OF ENVIRONMENTAL HEALTH SCIENCES

ANNUAL REPORT

July 1, 1967 through June 30, 1968

TABLE OF CONTENTS

Page

I. Index to Contract Narratives and Individual Project Reports 3

II. Organizational Chart.................................... 7

III. Office of the Director--Summary Statement................. 8

IV. Office of the Associate Director for Laboratory Research

A. Summary Statement.................................... 11

B. Contract Narratives.................................. 13

C. Individual Project Reports........................... 15

V. Animal Science and Technology Branch

A. Summary Statement.................................... 19

B. Branch Programs...................................... 20

C. Individual Project Reports........................... 26

VI. Cell Biology Branch

A. Summary Statement.................................... 36

B. Individual Project Reports........................... 38

VII. Pharmacology and Toxicology Branch

A. Summary Statement.................................... 58

B. Individual Project Reports........................... 60

VIII. Analytical and Synthetic Chemistry Branch

A. Summary Statement.................................... 66

B. Individual Project Reports........................... 68

IX. Office of Associate Director for Scientific Information--
Summary Statement... 82

X. Office of Associate Director for Demography--Epidemiology Branch--Occupational Studies Unit

A. Summary Statement.................................... 84

B. Individual Project Reports.......................... 87

INDEX TO CONTRACTS

By Contractor

Contractor	Contract No.	Title	Page
Duke University Medical Center	PH43-68-73	The Effects of Toxic Chemicals on Cell Membranes	13
University of North Carolina	PH43-68-74	The Subcellular Pathology of Heavy Metal Intoxication	14

INDEX TO INDIVIDUAL PROJECT REPORTS

Project Serial Numbers — Project Title — Page

Office of Associate Director of Laboratory Research

Project Serial Numbers	Project Title	Page
DEHS-OADLR-01	Mechanisms of Pulmonary Edema in the Albino Rat	15

Pathology and Physiology Branch

Project Serial Numbers	Project Title	Page
DEHS-PP-01	Effect of cytotoxic and environmental agents on the nucleolar activity of liver cells	17

Animal Science & Technology Branch

Project Serial Numbers	Project Title	Page
DEHS-AST-001	Interactions Between Chemicals and Viral Infections	26
DEHS-AST-201	The Effect of TEPA on the Immune Responses of Rabbits to an Attenuated Viral Vaccine	28
DEHS-AST-202	The Effect of Whole Body Gamma Radiation on the Immune Response of Rabbits to an Attenuated Viral Vaccine	30

Project Serial Numbers	Project Title	Page
DEHS-AST-301	Hydroponic Grass as a Supplement for Laboratory Animal Diets	32
DEHS-AST-302	Embryo Development as a Measure of Environmental Changes	34

Cell Biology Branch

Project Serial Numbers	Project Title	Page
DEHS-CB-001	Biochemical Effects of Alkylating Agents in Target Tissues	38
DEHS-CB-101	Survey of fungi for the presence of mycotoxins	41
DEHS-CB-102	Effect of colchicine on the fine structure of the dividing somatic nucleus in *Saprolegnia delica*	44
DEHS-CB-104	Action of fungicides on fungi	46
DEHS-CB-201	The effects of environmental agents on organogenesis	48
DEHS-CB-301	Nucleo-protein synthesis and metabolism with respect to the different induction stages of the cell replication cycle and the effect of specific environmental agents on nucleo-protein metabolism	52
DEHS-CB-302	The regulation of induction of drug and environmental agent metabolizing systems with respect to the cell replication	54
DEHS-CB-303	Effects of environmental agents on the biochemistry and biogenesis of mitochondria and other subcellular particles	56

Project Serial Numbers	Project Title	Page

Pharmacology and Toxicology

DEHS-PT-01	Teratogenic Responses to Benzhydrylpiperazine Compounds	60
DEHS-PT-02	General Testing for Teratogenic Activity	62
DEHS-PT-03	Interacting Factors in Pharmacology and Toxicology	64

Chemistry Branch

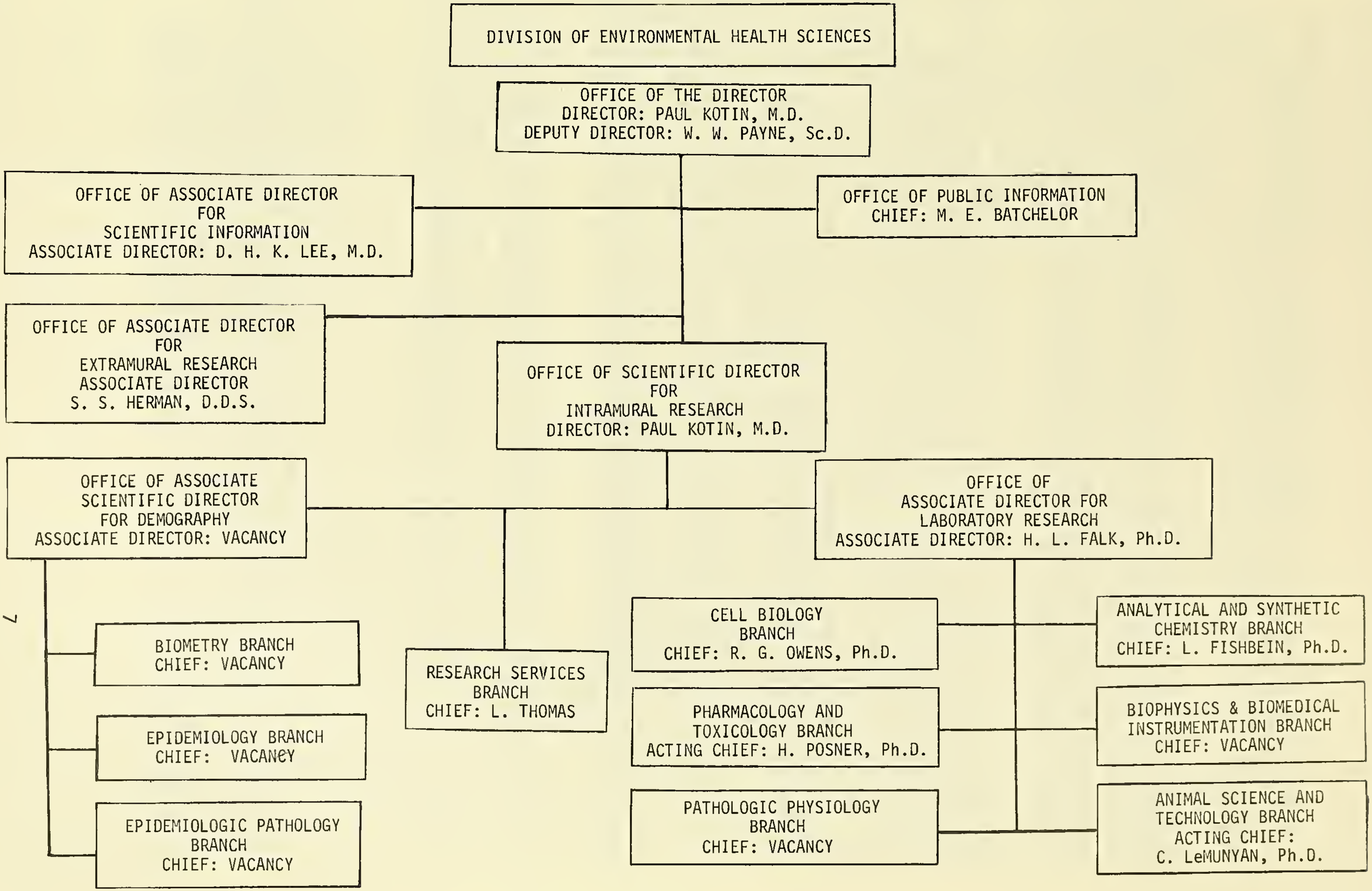
DEHS-ASC-001	Metabolism of Pesticidal Synergists	68
DEHS-ASC-002	Aflatoxin and Its Transfer in Milk as an Environmental Hazard	70
DEHS-ASC-003	Metabolism of Myristicin and Congeners	72
DEHS-ASC-004	Metabolism of Oil of Calmus and Its Constituents	74
DEHS-ASC-005	Effect of Environmental Parameters on Pesticidal Stability	76
DEHS-ASC-006	Development of Analytical Methodology	78
DEHS-ASC-007	Synthesis of Derivatives for Metabolic and Teratogenic Investigations	80

Epidemiology Branch, OASDD

Occupational Studies Unit

DEHS-E-01	Mortality Among Steelworkers	87
DEHS-E-02	Cancer Mortality Among Catholic Brothers and Sisters in Several Teaching Orders in the United States	90

Project Serial Numbers	Project Title	Page
DEHS-E-03	Epidemiological Study of Lung Cancer in Workers Exposed to the Inhalation of Zinc Chromate Paint in Airplane Construction and Maintenance Plants	92
DEHS-E-04	Epidemiologic Studies of Occupational Exposure to Cutting Oil Mists	95
DEHS-E-05	Health Hazards of Uranium Miners of the Colorado Plateau	97
DEHS-E-06	Study of the Cancer Experience of Non-uranium Hard Rock Miners in the Rocky Mountain Area	101


DIVISION OF ENVIRONMENTAL HEALTH SCIENCES
OFFICE OF THE DIRECTOR
DIRECTOR: PAUL KOTIN, M.D.
DEPUTY DIRECTOR: W. W. PAYNE, Sc.D.
OFFICE OF ASSOCIATE DIRECTOR FOR SCIENTIFIC INFORMATION
ASSOCIATE DIRECTOR: D. H. K. LEE, M.D.
OFFICE OF PUBLIC INFORMATION
CHIEF: M. E. BATCHELOR
OFFICE OF ASSOCIATE DIRECTOR FOR EXTRAMURAL RESEARCH
ASSOCIATE DIRECTOR
S. S. HERMAN, D.D.S.
OFFICE OF SCIENTIFIC DIRECTOR FOR INTRAMURAL RESEARCH
DIRECTOR: PAUL KOTIN, M.D.
OFFICE OF ASSOCIATE SCIENTIFIC DIRECTOR FOR DEMOGRAPHY
ASSOCIATE DIRECTOR: VACANCY
OFFICE OF ASSOCIATE DIRECTOR FOR LABORATORY RESEARCH
ASSOCIATE DIRECTOR: H. L. FALK, Ph.D.
BIOMETRY BRANCH
CHIEF: VACANCY
EPIDEMIOLOGY BRANCH
CHIEF: VACANCY
EPIDEMIOLOGIC PATHOLOGY BRANCH
CHIEF: VACANCY
RESEARCH SERVICES BRANCH
CHIEF: L. THOMAS
CELL BIOLOGY BRANCH
CHIEF: R. G. OWENS, Ph.D.
PHARMACOLOGY AND TOXICOLOGY BRANCH
ACTING CHIEF: H. POSNER, Ph.D.
PATHOLOGIC PHYSIOLOGY BRANCH
CHIEF: VACANCY
ANALYTICAL AND SYNTHETIC CHEMISTRY BRANCH
CHIEF: L. FISHBEIN, Ph.D.
BIOPHYSICS & BIOMEDICAL INSTRUMENTATION BRANCH
CHIEF: VACANCY
ANIMAL SCIENCE AND TECHNOLOGY BRANCH
ACTING CHIEF:
C. LeMUNYAN, Ph.D.

Summary Statement
Office of the Director, Division of Environmental Health Sciences
July 1, 1967 - June 30, 1968

During the past year the Director has been concerned with activation of the facility in North Carolina's Research Triangle Park. Primary attention has been devoted to expediting the acquisition of space for program implementation in accordance with plans and projections. In addition, the Director and staff have provided consultation and prepared numerous reports for the Office of Science and Technology, the Office of the Secretary, the Office of the Surgeon General, and the Congress.

The schedule for the acquisition and activation of facilities in the Research Triangle has been significantly delayed owing to the unique administrative requirements inherent in the activation of an NIH component away from the Bethesda campus and to budgetary constraints both within the Research Triangle Foundation and the Federal establishment. This, in turn, has had the effect of delaying professional staff recruitment and initiation of several components of the overall research program. The proximity of the Triangle universities has helped to minimize the impact of these adverse developments and is providing us with an alternative in our attempts to obviate the undesirable effects of delay wherever possible. Certain segments of the program, therefore, are being activated through cooperative and collaborative efforts with the three Research Triangle universities through support by the contract mechanism. Furthermore, to facilitate early program development and to assure operational flexibility in the face of budgetary limitations, the Division is reviewing its extramural program of support to assure relevance of its grant-supported activities to its mission. These activities include project grants, training grants, and support for broadly based, interdisciplinary Institute/Centers in academic institutions throughout the country.

The Scientific Directorate, consisting of the Deputy Director, Assistant to the Director, the Associate Directors of the Division, the Executive Officer, and the Public Information Officer, serves as the senior advisory body to the Director. In this capacity, it is concerned with the scientific content, quality, and orientation of the intramural and extramural programs. This is accomplished through periodic review of program.

Triangle Universities Liaison

A working agreement between the Division and the three Triangle universities has been agreed upon and is in operation. This has had the effect of granting to the Division and its staff many of the advantages of university affiliation including adjunct faculty appointment for scientific staff, use of library facilities by Division personnel, and visiting-scientist status for university faculty in the Division. Cooperative and collaborative research efforts are in progress, and future expansion is planned where indicated and feasible.

Consultative Services

The Division has been frequently called upon to provide consultation, guidance, and, occasionally, the preparation of staff documents for various echelons of the Federal establishment. A sampling of such consultation efforts includes:

1. For the Office of Science and Technology, a review of the criteria and standard for SO_2 in air.

2. For the Office of the Secretary, evaluation of the current state of research of the lung-cancer hazards to uranium miners and formulation of a maximal program to fill identifiable gaps and to update data of ongoing programs.

3. For the Office of the Secretary, provision of consultation and comment on new regulations on DDT, DDD, DDE in milk and milk products and the presentation of a report on the current status of the problem of pesticide hazards to man before National Research Council-National Academy of Sciences.

4. For the Office of the Surgeon General, preparation of position documents on smoking and health including critical review of current literature for updating of Report on Smoking and Health for the National Clearinghouse for Smoking and Health.

5. For the Office of the Secretary, review of the current status of the asbestosis problem.

6. For the Office of the Surgeon General, consultation and preparation of a staff document on potential hazards of Mace as used as a riot-control agent.

7. For hearings by the Consumer Subcommittee of the Committee on Commerce of the U. S. Senate, preparation of testimony on a less-hazardous cigarette.

8. For the Consumer Subcommittee of the Senate Committee on Commerce, evaluation of the Strickman Filter.

9. For the Office of the Surgeon General, a review and consultation on problems of drinking-water quality standards and the program of recycling of water.

10. For the Bureau of Disease Prevention and Environmental Control, preparation of criteria for carcinogenic hazards associated with particulate contamination of the air.

In addition, the Division has also responded to numerous inquiries from industry concerning such problems as:

1. Hazards associated with exposure to asbestos by occupational groups and the general population.

2. Potential hazards associated with glass fiber textiles.

3. The status of knowledge in relation to potential hazards with high nitrate concentration in foods, particularly baby foods.

4. Consultation with individual companies and industry-wide organizations in the steel, tobacco, and solid fuel industries.

The Division has participated in the sponsoring of conferences in academic institutions and has sponsored conferences in its own facility in North Carolina. Topics for these meetings included evaluation of the hazards of certain environmental contaminants and Chronic Disease Epidemiology; the latter resulted in several specific recommendations that have been or will soon be implemented.

The Division continues to emphasize its relationship to other components of DHEW, in particular, and the Federal establishment, in general, through development of its scientific information and communication program. Despite some of the uncertainties associated with the reorganization of the Public Health Service, there has been no interruption of this liaison.

In specific areas such as pesticides, air pollution, and occupational health, liaison has progressed significantly through exchange of documents and visits of administrative and program personnel. The responsibility of the Division to provide the scientific information about environmental health required in the standard setting, monitoring, and regulatory activities of HEW is recognized; this fact continues to contribute to the bases for the establishment of priorities and development of program.

In summary, the Division has, during the past year, created an ongoing intramural research program. At the same time, it has reviewed its extramural activities for the purpose of assuring clear relevance of extramural activities to the objectives and mission of the Division. It has also served as a consultative resource for a broad variety of environmental problems to program-related segments of the Federal Government and private enterprise.

SUMMARY STATEMENT
Office of the Associate Director for Laboratory Research
July 1, 1967 - June 30, 1968

During this fiscal year,the beginnings of laboratory research were launched at the National Environmental Health Sciences Center, the intramural activity of the Division of Environmental Health Sciences. The first and most important need was the recruitment of key scientific personnel to allow a coordinated and adequate growth rate of all scientific arms of the program. The logistics of implementing research in environmental health at the Center were the object of primary concern; only those capabilities needed at appropriate times and fitting into available space were deliberately selected.

Following successful recruitment for the Research Service Branch, the next most important area was the Animal Science and Technology Branch, which represents the backbone of the bioassay program of the Center. The Analytical and Synthetic Chemistry Branch simultaneously acquired sophisticated instrumentation as its chief was recruited. Finding the best supportive scientific personnel for this area remains a problem, but continuing attention is being applied, and successful resolution is expected.

In addition, several of the basic research arms of the program have been activated. Competent leaders in the fields of cell biology, pharmacology, pathology, and physiology have been recruited. However, when this core of scientists had been recruited, the need for adequate space for animal housing as well as bench research could not be met; and further recruitment was deferred to allow for the solution of the space problem.

During this year, a series of adaptations had to be made by the scientists at the Center to often changing conditions, which would have proved trying to any man, but which were tolerated and overcome by the group of scientists planning a program of research under existing environmental conditions.

Apart from the in-house program, described in more detail by the branch chiefs in their summary statements, and specified in individual reports, several important activities are being carried out with contract support. One deals with the effects of heavy metals, particularly lead, on biochemical function and mitochondrial structures of various organs of the rat; it is carried out at the University of North Carolina, under the leadership of Dr. Robert Goyer. Another deals with the interaction of pesticides with various natural and modified cell membranes; it is being conducted at Duke University under the direction of Dr. D. C. Tosteson. At North Carolina State University a contract-supported activity is being negotiated to explore the mycotoxin production by fungi that naturally contaminate tobacco. At the Triangle Research Institute, an in-depth study into the exposure of man to specific toxic metals is being supported.

In addition, several contracts are in the initial stages of negotiation to explore the hazard of lung cancer in uranium miners due to alpha emitters. These studies will stress the need to consider important secondary factors such as the effects of cigarette smoking and diesel-fume exposure, as they exist in the environment of the miners. Improvements in monitoring of the air in mines as well as screening of the miners for body burden and rate of elimination of alpha emitters will be carried out to allow for more adequate evalution of retrospective studies.

During the next few years the growth of the Center will, by necessity, be slow; but it will allow the most adequate and economic use of animal facilities and research bench space, as these currently represent the retarding factors in the growth of the laboratory research efforts of the National Environmental Health Sciences Center.

Duke University Medical Center, Durham, N. C. (PH-43-68-73)

Title: The Effects of Toxic Chemicals on Cell Membranes

Contractor's Project Director: D. C. Tosteson

Project Officer (DEHS): Paul Kotin, M.D.

Alternate Project Officer (DEHS): R. G. Owens, Ph.D.

Objectives: To characterize the interactions of various toxic environmental substances with cell membranes and to determine the kinds of interactions of greatest importance for specific compounds of interest.

Major Findings: A number of membrane systems have been used to evaluate effects of toxic compounds on membrane structure and function. These include lobster and squid axons for studies on nerve membranes, protozoan and red blood cells for studies on membranes of single cells, tissue cultures of cardiac and skeletal cells, and artificial bilayer membranes made from lipids from nerve and red blood cells. Studies thus far have dealt with DDT and some of its analogues and with pyrethrinoid compounds. All compounds tested have been found to affect the ion permeability of nerve membranes and the action potentials of the axon. Studies on structure-activity relations indicate rather rigid structural requirements for membrane effects. At least one pyrethrin analogue has been found to be more active than natural pyrethrins.

Significance to Bio-medical Research and the Program of the Division: Membranes separate the cytoplasm from its immediate environment, regulate the chemical composition of the intracellular fluid, and determine the action potentials in nerve and muscle cells. A number of toxins, particularly insecticides, have been shown to affect the function of nerve and muscle cells and to change the capacity of membranes to retain and to transport ions. This suggests that in some cases the primary target of environmental agents may be the cell membrane. The purpose of this program is to determine if this is the case and to elucidate the kinds of interactions that take place between cellular and/or membrane components and toxicants which affect nerve and muscle action.

Proposed Course: The membrane systems used in the present program afford an opportunity to study a wide variety of environmental agents which are known or suspected to affect membrane structure and function. Studies will be continued on DDT, dieldrin and pyrethinoids and their metabolites. In addition, as the work progresses, the studies will be extended to include oxides of nitrogen found in cigarette smoke; beryllium in the forms released from rocket engines; asbestos fibers of defined size, shape and composition; and cancer promoters, such as aliphatic and cyclic hydrocarbons.

Date Contract Initiated: January 16, 1968

Current Annual Level: January 16, 1968 through January 15, 1969: $108,620

University of North Carolina, Chapel Hill, N. C. (PH-43-68-74)

Title: The Subcellular Pathology of Heavy Metal Intoxication

Contractor's Project Director: Robert A. Goyer, M.D.

Project Officers (DEHS): William W. Payne, Sc.D. and Paul Kotin, M.D.

Objectives: To investigate the mechanisms whereby such heavy metals as lead, nickel, cadmium, and zinc interact with cellular organelles and affect metabolism. The basic approach is to correlate ultrastructural changes occurring in various organs with impairment or change in metabolism and function.

Major Findings: The project has been initiated by feeding lead to rats to determine the effect of ingestion of lead on the transport of amino acids by the proximal renal tubular lining cells of rats. The study of central nervous system effects has been initiated, but results are not yet available.

Significance to Bio-medical Research and the Program of the Division: One of the groups of environmental agents to be studied initially by the Division is heavy metals. Man is exposed to these agents through a variety of media including air, food, water, and working environment. Information on the mechanism of action on biological systems is urgently needed by control agencies for determining criteria and setting standards.

Proposed Course: Other metals will be added to the experimental protocol and long-term studies will be initiated as methodology is perfected.

Date Contract Initiated: January 16, 1968

Current Annual Level: $115,640

Serial No. DEHS-OADLR-01
1. Office of Associate
   Director of
   Laboratory Research
2.
3. Research Triangle Park,
   North Carolina 27709

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Mechanisms of Pulmonary Edema in the Albino Rat

Previous Serial Number: none

Principal Investigator: G. E. Thompson, Ph.D.

Other Investigators: none

Cooperating Units: none

Man Years:

Total: 1.5
Professional: 1.0
Others: .5

Project Description

Objectives

To ascertain some of the common mechanisms of the action of ozone and other toxic air pollutents in experimental acute pulmonary edema in the albino rat.

Major Findings:

It has been established that there is a seasonal variation of response of the albino rat to induction of pulmonary edema and that the variation is related to hair shedding and to sulfur deficiency. It has been demonstrated in this laboratory that the hyperthyroid rat is very susceptible to induction of acute pulmonary edema (APE). Undoubtedly catecholamines have a role in this reaction, because an overdose of epinephrine or norepinephrine will mimic APE. Alpha - adrenergic blockade prevents death and the accumulation of significant edema after an overdose of epinephrine. Pretreatment with a large amount of glucose prior to epinephrine lowers the mortality to 5% but allows tremendous edematous and congestive changes.

Significance to Bio-Medical Research and the Program of the Division:

At this point an interrelationship of diet, hormone action, and metabolism has been established as factors in the induction of APE. The importance of long-range exposure to environmental toxicants as in air pollution will be evaluated.

Proposed Course:

Ozone, a pulmonary edema inducer that occurs environmentally, will be used in the future to produce APE. It is expected that many of the baseline results found in the above mentioned experiments can be applied to the ozone studies. Also, the effect of body sulfur levels on glycogen and thyroxin levels will be examined in the next months.

Honors and Awards none

Publications:

1. Thompson, Geo. E., and Scheel, L. O., "Alteration of Lung Pathology from Diisocyanate by Glycemic or Sensitizing Agents," Arch Environ. Health, Vol. 16, pp. 363-370, March 1968.
2. Thompson, Geo. E., "Acute Pulmonary Edema (APE) in Rats, I. Seasonal Alteration of Response," Life Sciences, Vol. 6, pp. 2379-2386, 1967.

Serial No. DEHS-PP-01
1. Pathology and Physiology Branch
2.
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
February 1, 1968 through June 30, 1968

Project Title: Effect of cytotoxic and environmental agents on the nucleolar activity of liver cells.

Previous Serial Number: None

Principal Investigator: Anna Ottolenghi, M.D.

Other Investigators: Minerva Fields

Man Years:

Total: 2
Professional: 1
Other: 1

Project Description

Objectives:

To study early changes (30 minutes - 2 hours) in nucleolar morphology following administration of drugs generally acting as cytotoxic, cytostatic, or carcinogenic agents.

Methods Employed:

Supravital staining with Azure C (mono-methylthionine) of isolated liver cells; light microscopy.

Major Findings:

Aflatoxin B_1 causes a consistent dose dependent alteration of nucleolar morphology at 30 minutes after injection. These changes have been followed for 48 hours during which time they persist.

Comparable effects are seen with Dimethrin. The polycyclic hydrocarbons: 3-4-Benzpyrene, 3-Methylcholanthrene, 1,2,5,6-Dibenzanthracene have caused nucleolar changes less intense than those observed with Aflatoxin B_1. Alterations similar to those due to polycyclic hydrocarbons have been seen after administration of p-Dimethylaminoazobenzene.

Significance to Bio-medical Research and Programs of the Division:

The nucleolus is intimately involved with the process of RNA synthesis. Alterations in its morphology might provide a model for the study of mechanism of action of those agents which disrupt normal cellular equilibrium (carcinogens) and those which restore it (cytostatics).

Proposed Course:

A systematic survey of related chemical agents for the purpose of relating possible short-term response and long-term effects.

SUMMARY STATEMENT
Animal Science and Technology Branch
July 1, 1967 - June 30, 1968

A. Summary

The Animal Science and Technology Branch is responsible for the acquisition, quarantine, and conditioning of all biological models for the NEHSC; for the maintenance, husbandry, and veterinary care of all experimental colonies utilized by the NEHSC; for preparation and interpretation of macroscopic and microscopic specimens for histologic and pathologic study for the NEHSC; for special services relating to the animal sciences; and for the conduct of a broad but meaningful research program consistent with the mission of the Center; and to provide data pertaining to the animal sciences.

Primary efforts are made to meet the needs of the NEHSC by providing and maintaining all animals, animal facilities, equipment, and routine care of the experimental colonies. To support the basic service mission, ASTB conducts research and development and animal health programs. The research programs are designed to determine needs for providing and improving animal care--nutrition, facilities, equipment, husbandry practices, research methods; to develop data necessary to make more efficient use of manpower; and to furnish planning information for future animal facilities at the NEHSC.

Animal health programs conducted by ASTB veterinarians are designed to determine, protect, and improve the quality of the experimental animal colonies of the Center; and to aid in detection and disease control within the animal facility.

Individual scientists on the ASTB staff conduct related research programs within the scope of their professional discipline as a part of the overall NEHSC mission and ASTB research programs. The parameters of these programs vary from a study of the effects of acute and chronic exposure to pesticides and other organic compounds to studies of the effect of photoperiodicity and light intensity on reproductive physiology.

During the period covered by this report, the Animal Science and Technology Branch has accomplished its basic mission and contributed to the planning and development of future animal facilities for both interim and permanent sites. The program has been developed for a 15,000 square-foot, second interim animal facility; and members of the ASTB staff are currently consulting with members of the Research Services Branch, NIH facilities engineers, and the designated architectural firm to bring this animal facility to construction. Planning has also been initiated for the development of the Functional Program of Requirements for the permanent facility.

Although a variety of complex scientific and logistic problems constantly face the Animal Science and Technology Branch, most can be and are being met through the multi-disciplined efforts of the staff. Veterinary pathology services are contracted on a consultant basis. The most serious problem, which will not be resolved until the Phase II interim buildings are completed, is the lack of adequate animal and laboratory space to meet the needs of the NEHSC staff using animals and to provide for the development of ASTB professional staff respectively. However, these are situations which must be tolerated until future facilities are completed.

B. Branch Programs

Laboratory Animal Acquisition, Quarantine and Maintenance

A. Objective

To provide, quarantine, condition, and maintain experimental animals for the NEHSC staff.

B. Related Programs

Animals for experimental use by the scientific staff of the NEHSC are acquired as requested through purchase from reliable and recognized commercial animal breeders. The majority of these sources are selected from a list compiled by the Institute of Laboratory Animal Resources, NRC, NAS.

Upon arrival the animals are placed under a quarantine and health program, supervised by a staff veterinarian. The colonies are monitored by the ASTB microbiology, serology, and hematology sections, which are headed by staff veterinarians; and health control or improvement regimens are implemented, when prescribed, under their supervision.

The experimental colonies in use by the NEHSC scientific staff are continuously monitored for disease problems by the staff veterinarian responsible for this area. Forty-eight accessions consisting of 94 various kinds of samples--air, feces, nasal secretions, intestinal swabs, skin scrapings, etc.--have been examined for microbiological or parasitological pathogens. To date, 1,304 tests, including biochemical determinations, have been performed. Fifty fecal specimens have been submitted to Battelle Memorial Institute for Salmonella and Pseudomonas sp. surveillance. Highlights of the reporting period have been the identification of Salmonella javiana from a Marmosa mitis, Bordetella bronchiseptica from guinea pigs, Pasteurella multocida from rabbits, Diplococcus pneumoniae from a rat, and Demodex sp. from a gerbil.

Routine animal care and maintenance are provided by ASTB personnel who also assist the scientific staff by holding animals and otherwise helping in experimental manipulations. Humane disposition of animals in terminated studies is conducted under supervision of the veterinarian in charge.

C. Program Progress and Accomplishments

The first experimental animals to be acquired and maintained at NEHSC arrived early in the period covered by this report. Prior to this, a staff of caretaker personnel had to be recruited and trained.

A cooperative agreement between NEHSC and OPERATION BREAKTHROUGH, a local community action program, supported by the Office of Economic Opportunity and Labor Department, was instituted in July 1967; and ten individuals undertook training as animal technicians (Biological Aides). Developed and implemented by ASTB personnel, a training program provided 72 hours of classroom instruction in animal science and 1,356 hours of on-the-job training (including 380 hours of practical skill training) for each individual in this cooperative program. Trainees were also given 92 hours of classroom core training (interpersonal relations and problem solving) by the Extension Division of the University of North Carolina (UNC) under contract agreement with the New Careers program of OPERATION BREAKTHROUGH. On April 23, a joint graduation program was conducted for the enrollees, and diplomas were awarded by UNC. The graduates of this program constitute the majority of the present caretaking staff.

During this fiscal year, the ASTB has acquired, conditioned, and maintained 1,825 mice, 1,868 rats, 120 guinea pigs, 305 hamsters, 131 rabbits, 65 opossums, 2 marmosa, and 1 muskrat in support of the scientific programs of NEHSC.

In early March, a crash program was initiated to acquire and maintain adult opossums for use by one member of the scientific staff. The problem was complicated by lack of holding facilities and the request that acquisitions include as many pregnant females as possible. The latter requirement further stimulated immediate action because very little time remained in the spring breeding season for opossums. The Research Services Branch provided excellent service by constructing a half acre outdoor compound including quarantine and holding sections, wood feeders, and numerous nesting huts within a four-day period. ASTB staff members acquired scientific collector's permits from the North Carolina Wildlife Commission and visited Boy Scout troops in Cary and surrounding areas to encourage collection of the animals. By May 1,1965 adult animals had been collected. This quantity is estimated to provide an adequate supply for the program needs of this particular program until next January.

A related program to provide a smaller marsupial (Marmosa mitis) is under development. Twenty adult animals, 6 males and 14 females, were acquired from South America. Two litters have been born at NEHSC and are being reared in captivity. If a successful breeding method can be developed a breeding contract under NEHSC supervision will be sought for expanded production.

D. Problems

The Animal Science and Technology Branch has encountered increasing difficulty during the past year with regard to space. The present animal space is woefully inadequate to meet the needs of the NEHSC scientific staff. Cages and other equipment, which are in constant use, have been stored on the roof of an adjacent building in an attempt to utilize all available space for animals. This requires a trip to the roof by ladder once or twice a week for the necessary equipment to maintain operations.

The slowness with which the Phase II interim animal facility has progressed will have a deleterious effect on the magnitude of the overall NEHSC program. Until this building is completed, the Associate Director for Laboratory Research has determined there can be no additions to the Center's scientific staff who would require animals for use in their program.

E. Program Plans

Toward the middle of the next fiscal year, a program of recruitment and training will be initiated to provide animal-care personnel for the projected Phase II animal building. The experience of training personnel during the past year indicates a strong justification for acquiring recruits well in advance of program needs, if they are to be technically competent when facilities are ready. While fortunate to obtain enrollees through the OPERATION BREAKTHROUGH program this year, the increasing demand on labor resources due to expanded development in the Research Triangle Park area may make recruiting more difficult in the months to come.

Based on research, literature surveys, and site visits, planning for the permanent animal facility will gain momentum during the next year to insure incorporation of the most recent advances in animal science methodology and building requirements.

Histology-Pathology Services

A. Objective

To provide histo-pathology services for ASTB and NEHSC staff by preparation and interpretation of macroscopic and microscopic specimens.

B. Related Programs

The Animal Science and Technology Branch meets the needs of its own scientists and the Center's scientific staff through the operation of a histology laboratory and a consulting (contract) veterinary pathologist. The laboratory began operation in late September with one employee and at present, there are three technicians engaged in routine histological procedures.

C. Program Progress and Accomplishments

During the past few months of the period covered by this report, the ASTB histology lab has performed:

94 animal autopsies
281 autopsies cut-in and processed for paraffin work
3,508 tissue blocks processed and embedded
10,524 paraffin sections cut on the microtome
115 cases cut on the cryostat for frozen tissue work
4,028 hemotoxylin and eosin stains completed
1,744 special stains completed.

D. Problems

The space problem will be resolved when the NEHSC acquires Building 7.

E. Program Plans

The program will continue as outlined in Section B.

Special and Consultative Services

A. Objective

To furnish special services to the Center scientific staff and cooperating institutions in the Research Triangle area including: consultation on animal health and related fields; selection of proper animal models for maximum response to indicated stimuli; planning of animal facilities to comply with accepted standards and requirements and to meet the needs for the projected use of the facility.

B. Related Programs

Animal Science and Technology Branch veterinarians, physiologists, microbiologists, serologists, consultant pathologists, animal husbandmen, and other specialists furnish NEHSC investigators with a variety of information on normal animal anatomy and physiology, nutritional requirements, environmental requirements, husbandry practices, and disease problems.

Representatives of ASTB are also available to assist the four local universities and other scientific institutions with their problems as outlined above. At the same time, much expert advice is gained by NEHSC personnel relating to similar problems. During the past year, an informal seminar group composed of professional animal scientists at NEHSC, University of North Carolina, Duke University, and North Carolina State University was formed. A rotating seminar is conducted each quarter with the members of the visited institution assuming responsibility for the program.

Other close liaison with the universities is maintained through appointment of ASTB scientists by the local universities as adjunct professors. In return, ASTB has sponsored several NEHSC appointments of Guest Scientists from the university faculties.

C. Program Progress and Accomplishments

Although results are not readily measured, the consultative service furnished by ASTB to NEHSC and other investigators undoubtedly assists in helping in the design and evaluation of animal experiments. Frequent and repeated requests for service of this nature would seem to indicate its value.

The seminar group has proved extremely valuable during its first year of operation. It not only permits scientists from various institutions to become acquainted, but also permits individuals to share experiences relating to individual and group problems in animal science. The rotating site visit-host aspect encourages better understanding of the problems at hand.

The reciprocal appointments to university and NEHSC adjunct staff positions further enhance the NEHSC program. Cooperative and collaborative projects enable members of both to share experience and facilities. Participation by NEHSC members in academic activities such as teaching and co-chairing graduate programs provides a stimulus through interaction with the students, which is normally lacking in government research programs.

D. Problems

None

E. Program Plans

The program will continue as outlined in Section B.

Research Programs

A. Objective

To conduct a broad but meaningful research program consistent with the NEHSC mission.

B. Related Programs

Senior scientists of the Animal Science and Technology Branch are each pursuing independent and collaborative research programs relating to their own particular discipline within the scope of DEHS and NEHSC objectives. These studies, which are discussed in greater detail as Individual Project Reports, concern themselves with enhancing scientific knowledge in such areas as effects of whole-body gamma radiation on the immune response of mammalian models to attenuated viral vaccine, use of alkylating agents on the immune responses, interactions between chemicals and viral infections, development of pathogen-free fresh vegetable supplements for laboratory animal diets, and investigation of mammalian embryo development as a measure of environmental changes.

C. Program Progress and Accomplishments

All of the programs were started during the fiscal year and have not reached fruition. Basic techniques development, acquisition and calibration of equipment, and recruitment of qualified personnel constitute the major accomplishments in the program during the period covered by this report.

D. Problems

None

E. Program Plans

The program will continue as outlined in Section B.

Serial No. DEHS-AST-001
1. Animal Science & Technology Branch
2. Microbiology Section
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Interactions Between Chemicals and Viral Infections

Previous Serial Number: None

Principal Investigator: Joseph H. Gainer, D.V.M.

Other Investigators: T. Pry, M.S.; H. Givelber, M.D.; W. Capps

Cooperating Units: W. R. Bryan, Viral Oncology, NCI
R. Kinard, Viral Carcinogenesis, NCI
R. Manaker, Microbiology Section, NCI
F. J. Rauscher, Viral Leukemia and Lymphoma, NCI
E. D. Batte, N. C. State University, Raleigh
J. G. Lecce, N. C. State University, Raleigh
W. R. Harris, N. C. State University, Raleigh

Man Years:

Total: 2.5
Professional: 1.6
Other: 0.9

Project Description

Objectives:

To look for effects of interaction (particularly enhancing effects) between sublethal doses of certain chemicals and viral infections.

Methods Employed:

Mice are inoculated with various viruses and at specified intervals are treated with various chemicals. Observations are made for enhanced mortality, splenomegaly, tumor formation, depressed immune response or other altered disease response. Viruses used are influenze (PR8), pseudorabies (PRV), Rauscher leukemogenic (RV), Newcastle disease (ND), encephalomyocarditis virus, H1, and arboviruses. Chemicals being used are heavy metal salts, pesticides, and commonly used drugs.

Major Findings:

Sodium arsenite induces enhanced mortality to PRV, PR8, and ND virus; and it enhances splenomegaly in RV infections. Dieldrin similarly enhances mortality from PR8, ND, and PRV. Conversely, dieldrin and arsenite seemingly suppress mortality from arbovirus infections.

Significance to Bio-medical Research and Programs of the Division:

These findings indicate a potential hazard of the combined low-level effects of arsenic or dieldrin in enhancing viral disease response.

Proposed Course:

Continuation.

Honors and Awards:

None.

Publications:

None.

Serial No. DEHS-AST-201
1. Animal Science & Technology Branch
2. Serology Section
3. Research Triangle Park, N. C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Effect of TEPA on the Immune Responses of Rabbits to an Attenuated Viral Vaccine

Previous Serial Number: None

Principal Investigator: Scott L. Reynolds, D.V.M., NEHSC

Other Investigators: Joseph H. Gainer, D.V.M., NEHSC

Cooperating Units: None

Man Years:

Total: .8
Professional: .5
Other: .3

Project Description

Objectives:

To study the effect of an alkylating agent, used in insect eradication programs, on the immunological response of New Zealand White rabbits to attenuated myxomatosis viral vaccine.

Methods Employed:

Animals are treated with long term, low doses of triethylene phosphoramide (TEPA) by the subcutaneous route. An immunizing dose of vaccine is administered subcutaneously at an appropriate time. Animals are bled by the ear, vein, and heart. Complete blood and differential counts are taken on all animals. Serum is tested for agglutinating and neutralizing antibodies. Plaque reduction techniques are utilized as an assay method for neutralizing antibodies. Appropriate animals are then challenged with virulent virus, and studies are conducted in an attempt to correlate serological response with protection. The effects of these agents will also be studied on alteration in the infectious process of myxomatosis virus.

Major Findings:

Initial studies utilized 50 mg/kg of TEPA delivered in one dose and 5 mg/kg delivered in ten daily doses. This regimen proved to be 100% and 75% lethal, respectively. Subsequent studies, employing 5 mg/kg, 1.58 mg/kg, and .5 mg/kg every three days for a total of ten doses, showed TEPA to be non-lethal when delivered at these dose ranges and frequency. Animals on the 5 mg/kg dosing exhibited lymphopenia at day one and neutropenia on day four. Animals of the 1.58 mg/kg group exhibited slight lymphocyte depression on day four,accompanied by more significant neutrophile depression. The .5 mg group showed lymphopenia on day nine with no demonstrable neutrophilic changes.

Significance to Bio-medical Research and Programs of the Division:

TEPA is an agent of importance to environmental studies due to its potential use in insect eradication. It is generally known that many pesticides today may be found in food for human consumption, consequently adding to the total environmental stress on man. Triethylene phosphoramide (TEPA), due to its effect on mitosis of the lymphoid and myeloid centers, is an excellent model for immune suppression studies. Much work has been conducted with immune suppressant drugs utilizing soluble antigens and serological response. Of greater interest in this field are the effects of alkylating agents on the immune response to a particulate antigen and, more important, a live, attenuated viral vaccine. It has been shown in whole-body irradiation studies that opposite effects may be seen when studies were conducted using both soluble and particulate antigens. Due to the similarity of action of alkylating agents and irradiation, it is suspected that this may be true also for certain pesticides.

Proposed Course:

Continuation as described in Part B.

Honors and Awards:

None.

Publications:

None.

Serial No. DEHS-AST-202

1. Animal Science & Technology Branch
2. Serology Section
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Effect of Whole Body Gamma Radiation on the Immune Response of Rabbits to an Attenuated Viral Vaccine

Previous Serial Number: None

Principal Investigator: Scott L. Reynolds, D.V.M., NEHSC

Other Investigators: Don Wilholt, Ph.D., University of North Carolina, Chapel Hill, N. C.

Cooperating Units: School of Public Health, University of North Carolina, Chapel Hill, N. C.

Man Years:

Total: .6
Professional: .3
Other: .3

Project Description

Objectives:

To study the effect of short-term, whole-body gamma radiation on the immune response to attenuated viral vaccine.

Methods Employed:

Animals are exposed to short-term, whole-body radiation prior to being vaccinated with an immunizing dose of attenuated myxomatosis virus. Animals are being bled by the ear, vein, and heart. Complete blood and differential counts are taken on all animals. Serus is tested for agglutinating and neutralizing antibodies. Plaque reduction techniques are utilized as an assay method for neutralizing antibodies. Appropriate animals are challenged with virulent virus, and studies will be conducted to correlate serological response with protection. Viremia studies will also be conducted.

Major Findings:

At this time there are no findings to report.

Significance to Bio-medical Research and Programs of the Division:

Since the entry of the atomic era, many investigators have initiated various studies of the effect of this environmental stress on immune mechanism. Much of the work has produced conflicting results due to various sources of radiation, differences in dosimetry, and the use of antigens in different physical states. Much research is needed utilizing viral antigens where serological and protective responses are correlated; both long-term and short-term whole-body exposures employing a good attenuated viral antigen will be studied. It is also important to initiate studies involving combined effects whereby animals would be exposed to both ionizing radiation and pesticides at dose levels that normally would not produce immunosuppression when given alone.

Proposed Course:

Continuation.

Honors and Awards:

None

Publications:

None.

Serial No. DEHS-AST-301
1. Animal Science & Technology Branch
2. Reproductive Physiology Section
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Hydroponic Grass as a Supplement for Laboratory Animal Diets

Previous Serial Number: None

Principal Investigator: Cobert D. LeMunyan, Ed.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total: .5
Professional: .1
Others: .4

Project Description

Objectives:

To find a method for providing uncontaminated fresh vegetable material for use as a feed supplement for laboratory animals.

Methods Employed:

Various vegetable plants are being cultivated in a hydroponic medium under artificial lighting conditions. These will be compared with field-grown vegetables to determine whether the artifically cultivated crops differ significantly from the natural in terms of supporting general health of the animal, growth, reproductive capability, and lactation.

Major Findings:

Project under way.

Significance to Bio-medical Research and Programs of the Division:

The use of field-grown crops as a supplement for rodent diets presents a serious problem for research in environmental health. Field crops, such as kale, have been found contaminated with residues of pesticides and other chemicals, Salmonella sp, and other organisms. A suitable substitute must be found.

Proposed Course:

Continuation as described.

Honors and Awards:

None.

Publications:

None.

Serial No. DEHS-AST-302
1. Animal Science & Technology Branch
2. Reproductive Physiology Section
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Embryo Development as a Measure of Environmental Changes

Previous Serial Number: None

Principal Investigator: Cobert D. LeMunyan, Ed.D., NEHSC
Lester C. Ulberg, Ph.D., N. C. State University, Raleigh, N. C.

Other Investigators: Fuller Bazer

Cooperating Units: N. C. State University, Raleigh, N. C.

Man Years:

Total: .25
Professional: .10
Other: .15

Project Description

Objectives:

To determine whether early mammalian embryonic developmental changes can be characterized and defined as a measure of response to environmental changes.

Methods Employed:

Patterns of embryo development are being studied in a polytocous animal (mouse) subsequent to decreased blood supply to the uterus. Coagulation of the blood in the secondary veins and arteries of one uterine horn is accomplished on the day following mating while embryo development in the opposite uterine horn serves as control for the study. Embryo development in the two horns is determined on the third day post mating. A second aspect of this study will be to superimpose upon a developing litter, by surgical means, embryos from a second litter to test the hypothesis that the uterus makes its selection of embryos very early, perhaps before much differentiation occurs. Extra embryos will be transferred to uteri already containing embryos just before elongation of the trophoblast.

Major Findings:

New project.

Significance to Bio-medical Research and Programs of the Division:

This project is concerned with the details of a specific facet in the continuing search for an explanation of the relationship between the environment and an animal's ability to reproduce. The universality of early embryo death in the mammal has led to the speculation that physiological mechanisms are available to the animal to protect itself against pregnancy in stress situations. It should logically follow that the ability of the embryo to survive could be a sensitive measure of sudden change in environment.

Proposed Course:

Continuation as described.

Honors and Awards:

None.

Publications:

None.

SUMMARY STATEMENT
Cell Biology Branch
July 1, 1967 - June 30, 1968

The purpose of the program of the Cell Biology Branch is to clarify the long-range effects of noxious environmental agents on cells and tissues, to elucidate the fundamental mode of action of such agents, and to assess the long-term significance to toxicant-induced malfunctioning at specific metabolic sites on the long-range well-being of man. Biochemical changes already known to be induced by various toxicants include altered enzyme activity and profile, altered immune response, increases in certain enzymes, changes in hormone balance, and, in some instances, sterility, abortion, birth defects and tumor development. Because such effects involve numerous facets of metabolism and metabolic control, and because noxious agents are numerous and chemically diverse, the program of the Cell Biology Branch is necessarily broad.

Studies are being made on toxin production by fungi found on vegetables and other foodstuffs for human consumption. Ten such fungal extracts have been fed to Swiss albino mice. None were acutely toxic. However, one culture tentatively identified as Rhizopus sp. appeared to induce premature birth of offspring. A second experiment to confirm this is now underway. All cultures have been examined by thin-layer chromatography for the presence of mycotoxins aflatoxins in particular. While most of the cultures examined produce blue and green fluorescing compounds, no aflatoxins have yet been found. Cultures of numerous fungi are now on hand and will be tested for toxicity.

Preliminary studies indicate that captan at threshhold toxic dose-levels induces morphological changes in Helminthosporium sp. Further studies will be made to determine if morphological changes induced in various toxin-producing fungi by fungicides are accompanied by changes in toxin production.

Among vertebrates, a number of developing organs are dependent upon collagen fibrogenesis for normal differentiation and development. Collagen synthesis and fibrogenesis is inhibited by a number of toxic compounds, some of which occur in the environment. These compounds can be expected to affect the development of organs and structures dependent upon collagen fibrogenesis. Studies on chick-embryo integument show that β-aminopropionitrile inhibits collagen organization and subsequent development of feather follicles. This system is being used to study the effects of other compounds, including pesticides and heavy metals, on enzymatic and other processes involved in collagen synthesis and differentiation of cells and tissues.

Basically, all cell and tissue development is directed by the genome and the energy for development is dependent upon proper functioning and development of mitochondria and other organelles. Thus studies are underway to determine the possible role of histones in genome expression and the influence of environmental agents on the components involved in the mechanics of genome repression and expression. Enzyme induction also appears to be intimately related to the basic mechanisms of genome expression and protein synthesis.

Production of specific enzymes in specific cells and organs is a biochemical manifestation of the differentiation process. Moreover, enzyme induction constitutes a basic mechanism of defense against accumulation of foreign compounds. Environmental agents which affect protein synthesis and enzyme induction will cause serious disturbances in the body's defense mechanism. Thus, studies designed to clarify the induction process and the control systems involved are underway.

A number of environmental toxicants, including the insecticide rotenone, affect oxidative metabolism in the mitochondria. Other agents, particularly some carcinogens, affect the size and shapes as well as the functions of mitochondria. Thus studies are underway on the mechanisms of action of toxicants that interfere with mitochondrial function and alter the biogenesis and course of development of mitochondria, because these organelles are vital for the function and development of all cells and tissues.

Studies on other aspects of metabolism affected by environmental toxicants have been initiated also. These include effects of selected alkylating agents on synthesis of bradykinins in inflammatory reactions, on the synthesis and functioning of somatotropin and other peptide hormones, and on specific enzymes and metabolic processes.

Finally, a contract has been awarded for studies on the effects of pesticides and other environmental toxicants on cell membrane structure and function. Membrane systems under study include lobster and squid axons, protozoan and red blood cells, tissue cultures of skeletal and cardiac muscle, and artificial bilayer membranes made from lipids from nerve and red blood cells. Compounds under study include DDT and its metabolites, dieldrin and a number of pyrethrinoids. All of these compounds have been found to affect the ion permeability of nerve membranes and the action potential of the axon.

Serial No. DEHS-CB-001
1. Cell Biology Branch, DEHS
2. Cell Biochemistry Section
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
September 1, 1967 through June 30, 1968

Project Title: Biochemical Effects of Alkylating Agents in Target Tissues

Previous Serial No.: None

Principal Investigator: R. G. Owens, Ph.D.

Other Investigators: S. Reynolds, Ph.D.

Cooperating Units: Animal Science and Technology Branch

Man Years:

Total: 1.0
Professional: 0.5
Other: 0.5

Project Description

Objectives:

Alkylating agents exhibit in common the property of reacting with electron rich groups, such as NH_2, SH, and OH. Thus, they may be expected to react with numerous cellular components and at many sites in intermediary metabolism. Despite this, these agents generally affect one or a few organs or tissues preferentially, probably because of differential accumulation of the compounds in specific tissues. The purpose of this project is to determine which cells and tissues are primary targets for various alkylating agents at chronic threshhold doses and which enzymes and metabolic processes are most sensitive for each toxicant. Attention will be focused particularly on hormone synthesis and action, immune response mechanisms, and both feedback and genome enzyme regulation.

Methods Employed:

Rats are used as the test subject. Affected tissues and organs will be studied by use of radioisotopic metabolite tracers; gas, liquid and thin layer chromatography; electrophoresis and ultracentrifugation of proteins and peptides, and standard enzyme assay techniques or modifications as required

Major Findings:

As in other projects now in the initial phases of activation, a major effort has been devoted to establishment of laboratory facilities and acquisition of equipment. However, a group of Charles River rats have been under test for 4 months to establish time-dosage response curves for 4 test compounds: TEPA (tetraethylenephosphoramide), PMA (phenylmercuric acetate), captan {N-(trichloromethylthio)-4-cyclohexene-1, 2-dicarboximide], and 2-chloroethylmethane sulfonate. At present no ill-effects have been noted at the maximum dose of 25 mg/kg. Larger doses are being fed for the purpose of establishing the LD_{50} for oral administration of each toxicant in Wesson oil. Dosages for long-term studies will be adjusted in accordance with LD_{50} values for threshhold chronic effects.

Liver, spleen, lung, kidney, gonads, and smooth and skeletal muscle from control and TEPA-treated rabbits are presently being assayed for amino and nonamino acids, sugars, and other metabolites to establish baseline levels. TEPA levels were sufficient to induce reproducible drops in blood counts, but were otherwise subclinical.

Studies on the effects of alkylating agents on the synthesis of bradykinins in inflammatory reactions and somatotropin and other peptide hormones from toxicant-treated animals are underway and standardization of gel electrophoresis of these substances is in progress. Gel electrophoresis has been established as a satisfactory tool for study of these relatively small peptides.

Significance to Bio-medical Research and the Program of the Division:

As a class of chemical compounds, alkylating agents are widely distributed in the environment. Alkylating agents are constituents of fungicides, herbicides, insecticides, nematocides, rodenticides, and bactericides. Moreover, because of similarities in certain properties, they tend to interact jointly with electron-rich chemical groups within cells. Because many vital processes are dependent upon the function of SH, NH_2, OH and other electron-rich groups, it can be predicted that agents that react with and block the function of such groups will have drastic effects on the function of macromolecules particularly peptide hormones and antibodies and specific cells and tissues. Moreover, such groups are functional in protein synthesis-hence, in enzyme induction-and in enzymes which take part in feedback regulation through substrate accumulation and usage. Thus the action of alkylating agents could have far-reaching effects on the long-range function and replacement of specific cells, hormones, metabolism of foreign and natural molecules, and on the resistance of the organism to infection and disease. Elucidation of such interrelations through long-term, low-level exposures to this group of toxicants is the purpose of this project.

Proposed Course:

Charles River rats will be exposed by oral administration three times weekly to TEPA, phenylmercuric acetate, captan, and 2-chloroethylmethyl sulfonate at four dosages; e.g., the LD_{50} dosage and several lower dosages. The rats will be treated in sufficient numbers to allow for sacrifice of some at predetermined intervals. Hematological effects will be determined at each dosage level at one-month intervals. At three-month intervals a group of 10 rats will be given intravenously ^{14}C-labeled compounds and will be sacrificed one hour after injection. Changes in metabolism induced by each chemical at each dosage level will be determined in target tissues by analysis of metabolic intermediates. Where changes are found, more detailed studies will be made on individual processes and hormones in an effort to determine the precise site(s) of action of each compound at its threshhold concentration and to assess the role of malfunction at that site in the long-range well-being of the animal with respect to longevity, resistance to disease, tumor development, or other effects.

Serial No. DEHS-CB-101
1. Cell Biology Branch, DEHS
2. Natural Cell Products Section
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
September 11, 1967 through June 30, 1968

Project Title: Survey of fungi for the presence of mycotoxins

Previous Serial Number: None

Principal Investigator: Miriam K. Slifkin, Ph.D.

Other Investigators: R. G. Owens, Ph.D.

Man Years:

Total: 1.00
Professional: .60
Other: .40

Project Description

Objectives:

The purpose of this research is to determine whether or not toxins are produced by a variety of fungi that are found on agricultural products.

Methods Employed:

The isolates listed in Table I were taken from food products purchased locally. They have been tested or will be tested in these studies. In addition, Coriella granati (CG) and Helminthosporium turcicun var. Guatamala (HG) obtained from North Carolina State University are also being tested.

Table I. Fungi isolated from food purchased locally.

Isolate	Substrate	Isolate	Substrate
A1	Delicious Apple	P2	Pecans
[1]A2		[2]P3	
[1]A3		[2]H1	Kind of country ham
[1]C4	Cucumber	H2	
[1]P1	Pecans	H3	
		[1]H4	

[1] These organisms have been tested. [2] These organisms are being tested.

The organisms were grown on five different media -- cornmeal agar, malt extract agar, potato dextrose agar, Sabourad's agar, and Mycophil agar. The substrate that supported the greatest spore production was selected as the one to be used in the tests. Malt extract agar was found to be the best for most organisms and was used for these organisms and as control. The test organisms were inoculated onto petri dishes containing the chosen medium and allowed to incubate at 26°C for approximately two weeks. Seventy percent ethyl alcohol was poured over the surface of the culture and left for a minimum of one hour, a period sufficient to kill the organisms. The fungus and substrate were mixed with ground-up complete mouse food (B & G research animal laboratory food) and water until a homogeneous paste resulted. Small portions were pressed out and air dried so that hard pellets resulted. These were fed to Swiss albino mice.

Dry weights were made of petri dish cultures of A2, A3, C4, and P1 that were grown on malt extract agar. Five replicates were made of each. The following averages were obtained: A2 - 82.1 mgs, A3 - 80.0 mgs, C4 - 51.9 mgs,P1 - 45.1 mgs. On the basis of these, 1/10th of a culture grown on a single dish was added to 4 grams mouse food to give one days food for one mouse. (The fungi fed to the mice were not dried before being mixed with the regular f00d.)

For each organism tested four cages were used: Two with both male and female, one with a single male, and one with a single female.

A2, C4, H4, and P1 were treated for 30 days.

A3, P3, H1, CG, and HG were treated with a normal dose for 30 days and will be treated with a double dose for an additional 60 days. Autopsies were performed on a male and a female from each test series. Autopsies are also performed on the young that were born dead and recovered before eaten by their mothers.

Major Findings:

Control - mice fed commercial food - All mice appeared normal. One pair had 12 young, all normal, the other pair had 3 young - 2 normal, 1 born dead.

Media control - mice fed commercial food mixed with malt extract agar. All adults normal. All young were destroyed by their mothers.

A2, P1, C4, and H4 - no noticeable effect on parents or offspring.

P3 - males and females were not mated until four weeks after feedings began. So far, no ill effects have been observed.

A3 - adults were normal. The offspring were killed by the mother and some were eaten before they could be recovered. The following is an autopsy report given by Dr. Anna Ottolenghi:

"Seven newborn mice - the weight after several days of formalin fixation is between 1.25 gms and 0.80 gms. Four mice with lighter weight show absence of skin on the posterior surface of chest and neck (probably where mother killed them). External appearance - well developed. Visceral examination - all organs present in normal position, grossly equal in size in all 7 mice. Brain and cerebellum present and well developed. Essentially 'normal' baby mice. No microscopic examination."

H1 All young except two were destroyed by mother. Males and females were remated after birth of young. Two female offspring that are progeny from first mating are also being treated.

HG Ten young were born to one set of parents; at present, there are five survivors. To the second set, there are no survivors.

CG All young were eaten.

CG and HG in eating their young, did not kill them in the usual manner first, but rather began eating from the lower extremities upward while young were still living.

In all tests weights were recorded daily. The pattern was the same in all cases for males and non-pregnant females. There was a short period of weight loss - 2 to 3 days - then a slight gain for another 2 to 3 days and finally a leveling off. In the case of the pregnant females there was again a slight weight loss at the beginning and thereafter a continuous weight gain until birth. No distinction could be made from the record of weights between the test mice and the controls.

Significance to Bio-medical Research and Programs of the Division:

It is too early to determine the significance of the work done thus far; however, there is a possibility that CG and HG are injuring the mice in some fashion causing abnormal maternal behavior.

Proposed Course:

Many other fungi including species of Helminthosporium, Alternaria, and Fusarium will be tested. Those organisms that appear to produce toxins will be grown under a variety of environmental conditions to determine the optimum conditions for toxin production and conditions in which no toxins are produced.

The principal method of fungal control is by the use of fungicides. The toxins producing fungi will be given sub-lethal doses of fungicides to determine whether the pesticides alter toxin production.

Serial No. DEHS-CB-102
1. Cell Biology Branch, DEHS
2. Natural Cell Products Sectio
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
September 11, 1967 through June 30, 1968

Project Title: Effect of colchicine on the fine structure of the dividing somatic nucleus in Saprolegnia delica.

Previous Serial Number: None

Principal Investigator: Miriam K. Slifkin, Ph.D.

Other Investigators: None

Man Years:

Total: .5
Professional: .35
Other: .15

Project Description

Objectives:

Colchicine has been shown to stop nuclear division at a very specific point in mitosis by preventing the formation of spindle fibers. This drug has had the same effect on almost all organisms upon which it has been tested, ranging from the lowliest plants to man. One exception to this is found in the somatic nuclear division in the water mold Saprolegnia delica. Electron micrograph studies on untreated vegetative cells revealed that microtubules, the "backbone" of spindle fibers, are present. It is hoped that by comparing the effect of colchicine on the ultrastructure of the treated organism with that of the untreated, the function of microtubules will be demonstrated.

Methods Employed:

Saprolegnia delica was grown on hemp seed halves that were placed in an aqueous solution of 0.1% colchicine. After 3 to 4 days at 20°C sporangia had formed, and encysted zoospores were pushed out into the solution. An equal volume of 6% dextrose solution was added to induce germination. After approximately four hours, germ tubes were visible in most of the spores. The excess liquid was decanted off the germinating spores, and 2.5% gluteraldehyde added. The spores were centrifuged and washed three times in dilute salt solution. Post fixation was with 1% osmic acid. The cells were then dehydrated in an ethyl alcohol series and propylene oxide and embedded in epon.

Sections were cut on a Porter-Blum MT2 ultramicrotome with a diamond knife and were observed under an Hitachi electron microscope.

Major Findings:

It is premature to make definite statements; however, it does appear that microtubules are present within the nucleus. So far, none have been observed outside the nucleus.

Significance to Bio-Medical Research and Programs of the Division:

It is too early to establish the significance of this work, owing to the nature of the division process in the vegetative stage of *S. delica*. It should be useful in clarifying the function of microtubules and other components of the spindle apparatus.

Proposed Course:

The work will be continued in the same manner in hopes that the question of microtubule function can be resolved.

Serial No. DEHS-CB-104
1. Cell Biology Branch, DEHS
2. Natural Cell Products Sectio
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
September 11, 1967 through June 30, 1968

Project Title: Action of fungicides on fungi.

Previous Serial Number: None

Principal Investigator: Miriam K. Slifkin, Ph.D.

Other Investigators: None

Man Years:

Total: .1
Professional: .1

Project Description

Objectives:

The purpose of this research is to determine (1) the effectiveness of fungicides under laboratory conditions, (2) the build-up of fungicide resistance and adaptation or tolerance of organisms to high concentrations of the fungicides, and (3) the action of the fungicides on a microscopic and ultra-microscopic level.

Methods Employed:

Only preliminary studies have been made. Four varieties of *Helminthosporium sativum*, J115, S46, D26, and B8 that were obtained from North Carolina State University were used in this study. Captan and folpet were the fungicides.

Before the effect of the fungicides could be determined, it was necessary to learn the percentage germination under untreated conditions. Spores from stock cultures were scraped off with a loop and put into a serum bottle containing 10 ml sterile distilled water. This was mixed thoroughly; 1 ml portions syringed off and sprayed onto the surface of mycophil agar in petri dishes. These were incubated at 16°C for two days. The germinated and ungerminated spores were counted. Four replicates were made of each variety.

A drop of aqueous suspension of 1 mg/ml captan was placed in the center of plates containing spores of the four varieties of *H. sativum*. Four replicates of each was made and incubated at 16°C.

Pictures were taken under a Wild dissecting microscope at 100X. Polaroid 3000 film was used at a camera setting of 1/10 sec.

Major Findings:

Under untreated conditions the following percent germinations were obtained: J115-90%, S46-85%, D26-86%, B8-87%. Spore counts were not made of the captan treated plates. There was no germination in the area of the fungicide. The greater the distance from the captan, the greater the number of germinated spores. The germinated spores nearest the plates containing the captan were left in the incubator for 1 to 2 weeks. The organisms had grown over the surface of the medium. At low magnification (100X), all cultures looked normal.

Significance To Bio-medical Research and Programs of the Division:

These preliminary results indicate that the fungicide tested does affect the germination of *H. sativum* and that morphological changes occur.

Proposed Course: The action of many fungicides will be tested on a variety of fungi found on food products. Selections will be made for tolerance to the various fungicides. The changes involved in tolerance development will be clarified by physiological and biochemical studies. This knowledge should help us understand the more important properties in fungitoxicity.

Changes in morphology from the cultural to the ultramicroscopic levels will be followed by light and electron microscope studies. For these studies, sub-lethal doses of fungicides will be given so that changes in structure can be followed.

Serial No. DEHS-CB-201
1. Cell Biology Branch, DEHS
2. Cytology & Cytogenetics Sectio
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
January 1, 1968 through June 30, 1968

Project Title: The effects of environmental agents on organogenesis

Previous Serial Number: None

Principal Investigator: Elizabeth S. Stuart, Ph.D.

Other Investigators: None

Cooperating Units: For the studies concerned with ultrastructure, the facilities of the Institute for Biological Sciences, North Carolina State University, have been used. The IBS, for a plate charge, has supplied the facilities needed for preparation of materials and for electron microscopic studies.

Man Years:

Total: .5
Professional: .5

Project Description

Objectives:

In the broadest terms, the objective is to examine the effects of environmental agents on biological material with particular reference to a developing or embryonic system. These effects are being evaluated both in terms of experimentally induced abnormalities in organogenesis and in terms of specific cytotoxic effects.

(a) Long-Term Goals: Among the vertebrates, a number of developing systems are intimately dependent upon the presence of collagen - upon the occurrence of collagen fibrogenesis - for their normal development. Thus the present project is concerned with the effects of various agents on the appearance of collagen, e.g., its characteristic synthesis, organization, and/or distribution. The project is concerned also with integrating known concepts of developmental mechanisms with the abnormalities observed to result from experimental treatment. This last provides a means of understanding the effects of the toxic agents in terms of basic developmental mechanisms.

(b) Short-Term Goals: To date, the studies initiated have been aimed at evaluating the following points: (1) to what extent is developing chick skin a choice system in which to examine the effects of agents on normal organogenesis and on the appearance of organized collagen fibers? (2) Which methods of approach, in vivo or in vitro. are most efficient and suitable for such studies? (3) Does an agent known to have teratogenic effects and known to interfere with collagen fibrogenesis in other systems, interfere with collagen fibrogenesis and organogenesis in the embryonic chick integument? If it is established that a collagen inhibiting compound does interfere with normal integumental differentation, then it will be useful to examine the effects on skin of other compounds which are currently introduced into the environment. For example, the compound might chelate certain metal ions, some of which are known to be required by the enzyme system involved in collagen fibrogenesis.

The short-term objectives of the present investigation have also involved an examination of the cytological characteristics of embryonic chick skin: (1) an examination of control and treated skin in terms of their gross and microscopic characteristics and the alterations associated with exposure to the toxic compound. (This comparison will provide a basis for evaluating the cytotoxic effects of the agent.) (2) an examination of the ultrastructural characteristics of normal skin with particular reference to the presence and the characteristic organization of collagen fibers. (When completed, the information provided by this study will serve as a basis for later comparison with tissues exposed to various environmental agents. In addition, this ultrastructure study should provide information necessary to characterize the normal integumental fibroblast, e.g., condition and distribution of nucleoli, degree of E.R. development. Later, this information can be used for comparison with the characteristics of cells which are responding to various agents.)

Methods Used:

As a means of subjecting developing tissues to various agents, two methods have been employed: (a) in vivo exposure of the whole organism to the agent by injecting it into the chorioallantoic membrane. (b) in vitro exposure of a particular tissue, the embryonic integument, by incorporating the substance into the culture medium.

To study the fine structure of normal developing skin, the usual techniques associated with electron microscopy have been employed. A number of methods of fixation and staining have been tested to determine their suitability for the examination of both collagen fibers and cellular ultrastructure.

Major Findings:

(a) It has been shown that the development of the chick integument is susceptible to inhibition by an agent β-aminopropionitrile known to inhibit collagen fibrogenesis. Both organogenesis and the deposition of organized collagen appear to be inhibited as a result of exposure. Thus the developing integument can be used as a system in which to examine differentiation, the cellular toxicity, and the teratogenic effects of other agents.

(b) An approach using *in vitro* rather than *in vivo* methods of exposing tissues to the agents is indicated. Specific effects of the compound tested were obtained *in vitro*;and,under these conditions the response of the system is isolated from and, therefore, not complicated by the remainder of the embryo. However, the observations from earlier *in vivo* studies suggest that at later stages of the project, it may be desirable also to test compounds *in vivo* in order to examine the following: (1) the teratogenic effects of the compounds on other developing tissues; and (2) the means by which the whole embryo deals with the agent which was introduced.

(c) The ultrastructural evidence obtained to date, though incomplete, indicates that the fibrous material appearing in the dermis of the differentiating integument is primarily collagenous and that at the ultrastructural level, its distribution is non-random. Further data are necessary, however, before the specific ultrastructural organization can be described. In addition, it appears that the organization of collagen fibers into bundles bears a specific relationship to the organ-forming population of dermal cells.

To complete these ultrastructure studies, it appears that the use of routine, fine-structure methods of preparation and staining will be sufficient. However, use of a scanning microscope for the further study of the ultrastructure detail of fiber organization, is strongly indicated.

Significance to Bio-medical Research and to the Program of the Division:

Evidence from other studies presented in the literature and evidence obtained by this investigator in earlier studies suggest that differential distributions of collagen play a significant role in the morphogenesis of a number of tissues, e.g., skin, pancreas, salivary glands. This is in addition to its significance for bone, cartilage, and joint growth and maintenance. Thus, studies concerned with the normal and abnormal appearance of collagenous material are extremely relevant to the general problem of environmental health and the effects of toxic agents.

In broad terms, the interest of the Division's program centers on the general toxic and teratogenic effects of compounds present in the environment. The findings from the short-term experiments have indicated that the normal development of a particular tissue system can be altered by utilizing a compound interfering with collagen fibrogenesis. A number of compounds, including some commonly used as pesticides, also may be expected to interfere with collagen synthesis either directly or via their breakdown products. The present studies, therefore, provide a baseline to which the effects of these other agents can be compared. As a result, studies of this embryonic system and the effects of agents on it will provide information concerning collagen fibrogenesis, its role in organogenesis, and the cytotoxic and teratogenic effects of various agents.

Proposed Course:

The course of further research will follow the long-range goals set forth earlier. Agents will be chosen which might be expected to effect collagen synthesis. In this way three categories of information can be obtained: (a) the general cytotoxic and teratological effects of various agents, (b) the specific effects of these agents on collagen synthesis, and (c) the basic mechanisms of collagen synthesis and organization in development.

In addition, use of chick skin as a test system provides another parameter, that of biological pattern. Feather germs normally differentiate in a specific temporal and spatial sequence. Thus, any interference by the agents with this patterned distribution of organs will be readily evident.

Further research will also include an examination of the ultrastructural changes in cells and collagen fiber distribution associated with the treatment of tissue with various agents.

As presently planned, the research program outlined above will be interrupted by a temporary absence beginning in June 1968 and extending until August 1969.

Serial No. DEHS-CB-301
1. Cell Biology Branch, DEHS
2. Biochemistry Section
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Nucleo-protein synthesis and metabolism with respect to the different induction stages of the cell replication cycle and the effect of specific environmental agents on nucleo-protein metabolism.

Previous Serial Number: None

Principal Investigator: Judson W. Spalding, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total: 2
Professional: .65
Other: 1.35

Project Description

Objectives:

The objectives are (1) to investigate the mechanisms by which nucleo-protein synthesis and metabolism are induced and regulated to gain insight into the depressive and repressive mechanisms of gene expression; and (2) to investigate the effect of specific environmental agents on nucleo-protein metabolism during various induction stages of the cell replication cycle.

Methods Employed:

(a) Basic nucleoproteins (histones) were isolated from selected tissue culture cell lines and animal organs by several preparative procedures and were compared to establish meaningful criteria for investigating basic nucleo-protein metabolism.

Analysis of these proteins by polyacrylamide-gel electrophoresis was used as a basis for comparison and subsequent characterization.

(b) A study of the cell replication cycle of several tissue culture lines has been initiated. Methods for staging and controlling the replication cycle of these cell lines are being studied and evaluated to provide cell systems of differing biological characteristics in which basic nucleoprotein metabolism may be compared.

Major Findings:

A comparison of basic nucleo-proteins isolated from Hela cells, Syrian Hamster embryo cells, and rat liver by three preparative methods revealed no significant qualitative or quantitative differences. Qualitative differences were noted in the basic nucleo-proteins isolated from young adult rat thymocytes; however, these differences proved to be dependent on the preparative method used for basic nucleo-protein isolation. The significance of this observation is under investigation.

Significance to Bio-medical Research and the Program of the Division:

The characterization of basic nucleo-proteins (histones) has received a great deal of attention during the last few years. The above findings, together with those from other laboratories indicate that there are close similarities among this class of proteins obtained from a wide range of animal tissues and species. Basic nucleo-proteins from some plant species are also similar. This has provocative implications with respect to evolution. More importantly, these findings should stimulate interest and shift emphasis toward the study of the regulation of basic nucleo-protein metabolism which perhaps is more closely related to the regulation of gene expression.

Proposed Course:

(a) The metabolism and synthesis of several classes of basic nucleo-protein will continue to be investigated to determine the existence of a temporal relationship between any specific stage of the cell replication cycle and basic nucleo-protein metabolism.

Special emphasis will be placed on the early interphase period of the cell cycle, because this is the stage which is most analogous to the functional stage of cells comprising differentiated tissues.

The effect of selected environmental agents on basic nucleo-protein metabolism at various induction stages of the cell replication cycle will be investigated.

(b) An attempt will be made to establish several more tissue culture cell lines of widely different biological characteristics for further comparison.

Serial No. DEHS-CB-302
1. Cell Biology Branch, DEHS
2. Biochemistry Section
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The regulation of induction of drug and environmental agent metabolizing systems with respect to the cell replication cycle.

Previous Serial Number: None

Principal Investigator: Judson W. Spalding, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total: .65
Professional: .35
Other: .30

Project Description

Objectives:

The objectives are to establish a tissue culture system (1) in which there are retained some of the significant functional characteristics of the tissue of origin, and (2) in which detoxification or metabolism systems for specific environmental agents (pollutants) can be induced.

When such a tissue-culture system has been established, the replication cycle will be evaluated in order to determine that stage of the life cycle when cells are most susceptible or refractory toward the inductive process by specific stressors of the extra-cellular environment.

Methods Employed:

A procedure for establishing a primary Syrian Hamster embryo culture system which is subject to induction by carcinogens has been initiated. The growth characteristics of this culture system with respect to the different cell types present is currently under study.

Major Findings:

Since this project is in the initial stages of development, no major findings will be reported.

Significance to Bio-medical Research and Program of the Division:

A tissue-culture system which retains significant characteristics of the tissue of origin and which is responsive to induction by extracellular agents provides a valuable biological system in which the inductive process may be studied at the molecular level. Such a defined biological system would be especially relevant to investigatons concerned with the metabolic process by which environmental agents (pollutants) effect their toxicity or by which all systems are able to resist the toxicity of environmental agents.

Proposed Course:

The proposed course is to define further the growth characteristics of the tissue-culture system under current study and to develop a method for distinguishing the specific cells or cell types which are capable of responding to a specific inducer.

When the responsive cell system has been characterized, studies on the regulation of the inductive process will be carried out at the molecular level.

Development of new methods and techniques for establishing more appropriate and responsive tissue culture systems will be pursued.

Serial No. DEHS-CB-303
1. Cell Biology Branch, DEHS
2. Biochemistry Section
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Effects of environmental agents on the biochemistry and biogenesis of mitochondria and other subcellular particles.

Previous Serial Number: None

Principal Investigator: B. Dean Nelson, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total: 2.3
Professional: 1
Other: 1.3

Project Description

Objectives:

(a) To elucidate the action of chemicals which interfere with the biogenesis of mitochondria and other subcellular organelles.

(b) To study the effects of toxic agents on mitochondrial oxidative phosphorylation and to elucidate their mechanism of action.

Methods Employed:

Protozoan cells are being adopted as test organisms because: (1) They can be grown under highly defined conditions thus allowing precise manipulation of their chemical environment; (2) With them, large quantities of a homogeneous cell type can be obtained for biochemical studies; (3) They can adapt to and metabolize drugs and other toxic compounds such as aflatoxins; (4) Like mammalian cells, protozoa are morphologically and biochemically complex; but, unlike mammalian cells, protozoa can be experimentally manipulated in highly defined environments during periods of rapid cellular growth; and (5) Cell division can be synchronized. Synchronous division is desirable for the study of organelle replication. Biochemical studies on protozoa will utilize the techniques of differential and density gradient centrifugation, polarographic and Warburg respirometry, spectrophotometric studies on enzyme rate reactions, and chromatographic and radioisotopic procedures for purifying and measuring the synthesis of nucleic acids and proteins.

Major Findings:

Prerequisite for studies on mitochondrial biogenesis is the development of methods for the isolation and characterization of functional mitochondria from the protozoan Euglena gracilis. Euglena electron transport appears similar to that in mammalian mitochondria. Euglena mitochondria oxidize reduced nicotinamide adenine dinucleotide, succinate, alpha-ketoglutarate, glutamate, alpha-glycerol phosphate, ascorbate, pyruvate, malate, and beta-hydroxybutyrate. Oxidation of NADH, but not succinate, is inhibited by rotenone, indicating that the site of action of this insecticide is similar in Euglena and rat mitochondria. NADH oxidation by Euglena mitochondria is inhibited 50% by concentrations of 1 μg rotenone/mg mitochondrial protein. Amytal, a barbiturate which inhibits NADH oxidation at the same site as rotenone, has no effect on Euglena mitochondria at concentrations up to 50 μg/mg mitochondrial protein. ATPase, an enzyme complex necessary for oxidative phosphorylation, is also present in Euglena mitochondria. As in rat mitochondria, Euglena ATPase is activated by the uncoupling agent 2,4-dinitrophenol, but unlike rat mitochondria, activation shows an absolute requirement for a divalent cation. Mg^{+2} and Mn^{+2} give maximal activation, while Co^{+2}, Zn^{+2}, Ca^{+2}, and Fe^{+2} give lesser stimulation and Mo^{+2} and Cu^{+2} produce no stimulation. Distribution studies on Euglena cells indicate that as in mammals the enzymes succinic dehydrogenase, succinic oxidase, and NADH oxidase are found only in the mitochondrial fraction, whereas malic dehydrogenase is found in the soluble fraction as well. Unlike mammalian mitochondria, substrate oxidation in Euglena does not appear to be under control of ADP. Experiments are currently being conducted to investigate the possibility that a "coupling protein" which is necessary for such control is solublized during preparation of the mitochondria.

Significance to Bio-medical Research and the Program of the Division:

Findings indicate that, in general, Euglena mitochondria are functionally similar to mammalian mitochondria. This similarity of function and structure (literature reports), coupled with the fact that Euglena can be easily grown on highly defined chemical media, suggests that this organism can be used advantageously to study replication and function of subcellular particles during cell growth in an adverse chemical environment.

Proposed Course:

Studies to characterize Euglena mitochondria and to test the effects of antibiotics and carcinogens on their function and biogenesis will continue. Experiments are now being initiated to characterize the nucleic acids of Euglena mitochondria and to study the effects of chloramphenicol on nucleic acid synthesis. The antibiotic chloramphenicol preferentially inhibits mitochondrial protein synthesis.

Summary Statement
Pharmacology and Toxicology Branch
July 1, 1967 - June 30, 1968

The goals of the Pharmacology and Toxicology Branch are fivefold. First, to identify the effects of certain environmental agents on living systems; second, to assess the significance of the initial interactions in terms of potential or actual end results, both detrimental or potentially beneficial; third, to investigate the mechanisms by which the initial interactions produce the end results; fourth, to seek practical means of control over the sequence of events so that one might cancel, potentiate, or otherwise modify the final event; and fifth, to be able to predict and verify the effects of other agents that might be harmful to man.

The program is designed to be not only that of the acute and the more obvious, but also of the chronic, the less obvious, and the unexpected. By their nature, acute effects are relatively easy to detect and to associate with a causative agent. Chronic effects are not only more difficult to associate with a specific causative agent, but they are also highly modifiable due to secondary interactions. Time, in the chronic effect, introduces the potentiality of greater variation in the type of manifest response.

The activities of the Branch began in September 1967. Since then, four activities have occupied us: 1) the construction and equipment of the laboratory and animal rooms; 2) recruitment and training of personnel; 3) establishment of associative relationships, both within and outside of NEHSC; and 4) the beginning of the research programs.

Without elaboration, it need only be said that the equipment and construction of the laboratory and animal rooms involved considerable time and that the recruitment and training of personnel has been an ongoing process. Additional personnel will arrive shortly. Training of the personnel involved the following: 1) the mating of animals and the accurate determination of the occurrence of mating; 2) examination of the fetoplacental unit for gross malformations as well as for skeletal system and internal organ defects; 3) quantification of the extent of several defects; 4) the operation of laboratory equipment; 5) familiarization with the aims of the research.

With respect to associative relationships, Dr. Posner received an adjunct appointment at Duke University (Associate Clinical Professor, Department of Physiology and Pharmacology), and serves as a member of the Library Committee (NEHSC). Mr. Easterling is a member of the Safety Committee (NEHSC) and Mr. McDowell is a member of the Recreation and Welfare Committee (NEHSC). Dr. Posner presented two lectures this year, the first entitled "Chemical Alteration of Phenotypes in Animals" (NEHSC), and the second entitled "Benzhydrylpiperazines and Cleft Palate" (Dental Research Center, School of Dentistry, University of North Carolina).

Three lines of research were initiated: 1) an extension of research begun at Bethesda on teratology resulting from the administration of compounds of the benzhydrylpiperazine series; 2) teratologic testing of additional compounds which have either not been tested previously or which are chosen in an attempt to confirm the initial reports of others; and 3) the beginning of a program on interacting factors in the pharmacology and toxicology of certain environmental agents. To date, components of two natural product series and selected compounds from among the pesticides (fungicides and herbicides) have been tested. In addition, a MEDLAR'S bibliography was obtained ("Immuno-Pharmacologic Aspects of Maternal-Fetal Exchange"). It was indexed by us, for our use.

Thus, despite the inevitable problems associated with the initiation and creation of an effective laboratory operation, the mounting of a research program of excellence has begun. We look forward to the further development of our efforts, and present in the following pages, our results to date.

Serial No. DEHS-PT-01
1. Pharmacology and Toxicology Branch
2. Growth and Development
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Teratogenic Responses to Benzhydrylpiperazine Compounds

Previous Serial Number: See NIDR-38 (65)

Principal Investigator: Dr. Herbert S. Posner

Other Investigators: None

Cooperating Units: None

Man Years:

Total: 0.3
Professional: 0.1
Other: 0.2

Project Description

Objectives:

In previous work the teratogenic effects of five benzhydrylpiperazine drugs were studied, mainly following their administration from days 12-15 of gestation. Here, chlorcyclizine was administered earlier or later in gestation, at doses near or slightly above the ED_{50} dose for cleft palate formation (as determined by administration from days 12-15). Further teratology and further insight into the mechanisms of the teratology, already observed, were sought.

Methods Employed:

Chlorcyclizine was administered orally to pregnant Sprague Dawley rats. At day 20 of gestation, the fetoplacental unit was examined for gross and skeletal malformations.

Major Findings:

Chlorcyclizine, administered from days 14-16 of gestation, at a dose of 70 mg/kg, yielded a high incidence of fetal thoracic edema. Cleft palate did not occur. It would appear from this and previous data that formation of edema does not require the existence of a cleft palate. This is of importance because the converse, that the production of cleft palate may be dependent upon the presence of thoracic edema occurring at an appropriate stage of development, remains a tenable hypothesis.

Chlorcyclizine, administered from days 1-8, 6-9, 8-9, or 8-11, at doses of 50 or 70 mg/kg, also yielded few cleft palates, as expected. However, there were resorptions, runts, and effects on the placenta (enlarged placentas, hemorrhaged placentas, degenerative cysts of the placental villi, and a pair of conjoined placentas). Two normal size fetuses presented dead and with massive hemorrhage. Four fetuses, in two litters, had mild to severe degrees of wrinkled skin, extended head, phocomelia, stumpy tail, malrotated limbs, and micrognathia. It would appear that one of the major effects of chlorcyclizine at all times of gestation is an effect on the fluid balance of the placenta and fetus.

Significance to Bio-medical Research and Programs of the Division:

The benzhydrylpiperazine series of compounds produce in the developing fetus an effect--edema--which has now been found with an environmental agent, 2,4,5-T. This effect will undoubtedly be found with many other compounds. A comparison of the edema and the other defects or malformations observed will hopefully lead to an understanding of both the mechanisms of fetal edema formation and the mechanisms of some forms of teratogenesis.

Proposed Course:

The project will continue. Teratogenesis due to the benzhydrylpiperazine series of compounds will be compared with the fetoplacental effects of other agents under study.

Serial No. DEHS-PT-02
1. Pharmacology and Toxicology Branch
2. Growth and Development
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: General Testing for Teratogenic Activity

Previous Serial Number: None

Principal Investigator: Dr. Herbert S. Posner

Other Investigators: None

Cooperating Units: Animal Science and Technology Branch, Analytical and Synthetic Chemistry Branch, NEHSC

Man Years:

Total: 1.3
Professional: 0.3
Other: 1.0

Project Description

Objectives:

The objectives of the project are to identify the effects of selected environmental agents on the fetoplacental unit.

Methods Employed:

In general, chemicals are administered orally in an appropriate solvent, to pregnant animals (rats and mice, at present). Most frequently, the fetoplacental unit is examined at day 20 of gestation. Gross abnormalities, skeletal malformations, and internal organ defects are sought. Controls for each of the solvents or suspending media used are investigated.

Major Findings:

The oil of two varieties of calamus are being studied, as are partially purified fractions, obtained by distillation, and some of the components which are available in pure form. One of the distillation fractions yielded a high incidence of placental effects (fatty placenta, enlarged placenta, and a pair of double placentas). A low incidence of resorption and skeletal defects was obtained.

In initial studies, myristicin (a component of oil of nutmeg) yielded a low incidence of resorption only.

An herbicide, 2,4,5-T, killed most of the fetuses at higher doses and yielded small fetuses and fetal edema at somewhat lower doses. Further studies are in progress.

Captan and Difolatan (fungicides) and Sevin (an herbicide) present solubility problems. New solvents and suspending agents are now being investigated before further teratogenic testing is undertaken.

Significance to Bio-medical Research and the Programs of the Division:

The project attempts to define the effective dose range and the types and extent of the effects of environmental agents on the developing fetoplacental unit. Identification will then present a base for more detailed investigation of the effects that are deemed important.

Proposed Course:

The project will continue. Additional types of effects on the fetoplacental unit will be sought, as the effects are deemed significant and as the methods become feasible. Additional solvents and suspending media for the compounds are being investigated.

Serial No. DEHS-PT-03

1. Pharmacology and Toxicology Branch
2. Growth and Development
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Interacting Factors in Pharmacology and Toxicology

Previous Serial Number: None

Principal Investigator: Dr. Herbert S. Posner

Other Investigators: None

Cooperating Units: None

Man Years:

Total: 0.3
Professional: 0.1
Other: 0.2

Project Description

Objectives:

Many factors can affect the response of an organism to an administered agent. Such factors as already clearly defined are: sex, genetics, nutritional status, state of health, co-administration of other agents, age, hormonal status, crowding vs. isolation, season, time of day, etc. It is the purpose of this project to identify interacting factors where present and to study the nature and potential detrimental or beneficial effects of such interactions.

Methods Employed:

In this first example of a potential interacting factor in pharmacology and toxicology, noncutaneous, visceral sites of pigmentation were sought in laboratory-type animals. Where found, the extent of pigmentation was investigated as a function of sex, coat color, and prior administration of DOPA.

Major Findings:

Confirmation was made of the specific pattern of melanin coloration in the meninges of the brain of a strain of rabbit (Weil-Malherbe, Posner and Bowles: J. Pharmacology and Experimental Therapeutics, 132, 278 [1961]). Presence of the pigmentation was independent of sex, but appeared, within the strain, to be dependent upon coat color. In some cases, the pigmentation covered almost all, or alternatively, little of the meninges; and then the pattern was not as apparent. The pigmentation appeared to be darker after the administration of DOPA. It was also seen on occasion in the meninges of the spinal cord, although no pattern was evident. Pigmentation was not seen in the abdominal or thoracic viscera. It was also not found, in similar sites, in other species examined to date.

Significance to Bio-medical Research and the Programs of the Division:

Many factors can predispose an organism toward unfavorable or favorable response toward an administered agent, as stated above. Pigmentation, whether due to melanin or to some other chromogenic substance, may be such a factor. Melanin, for example, can protect against irradiation and can take part in oxidation-reduction reactions. As such, depending upon the availability of a reproducible animal model, a potential role of pigmentation or the lack of pigmentation can be investigated, as can other factors that will be considered.

Proposed Course:

The project will continue. Additional species of animals will be investigated for noncutaneous sites of pigmentation. Other factors, as listed above, will also be considered with respect to their potential involvement in differential responses to administered chemicals.

SUMMARY STATEMENT
Chemistry Branch
July 1, 1967 - June 30, 1968

The programs of the Chemistry Branch are designed to conduct, support, and augment research related to the effects of a broad spectrum of environmental agents, e.g., pesticides, food additives, trace metals, and other pollutants in air, water, and food, including the study of their metabolic and degradation products. The Branch is concerned with the analysis of multiple components in an effort to elucidate synergistic effects.

The Branch is engaged in the standardization, improvement, and development of new analytical techniques for the determination of specific chemicals utilizing analytical spectroscopic instruments and chromatographic procedures.

Synthetic chemistry procedures are also employed for both the preparation of required intermediates and confirmation of identity of isolated metabolites and degradation products.

During the present fiscal year, a considerable period of time has been spent on the immediate necessities of the recruitment of personnel and the procurement, installation, and performance appraisal of equipment as described above.

Programs that are in progress include:

(1) The development of analytical methodology, primarily thin-layer and gas chromatographic techniques for the analysis of isomeric allyl, propenyl, and dihydro derivatives related to the components of the oils of calamus and nutmeg; of the pesticidal isomeric chlorophenols by preparation of their respective isomeric fluorosulfonyl benzene chlorophenyl sulfonates; of chemosterilants Tepa and Thio-tepa from mammalian blood; and of aflatoxins using pyrolytic or derivative techniques.

(2) The synthesis of required intermediates for metabolic and teratogenic studies, as well as for confirmation of structure, include the epoxides of the fungicides Captan and Difolatan; and the naturally occurring isomeric allyl and propenyl trimethoxy benzenes, elemicin and isoelemicin.

(3) The unequivocal separation and identification of the components of the oils of calamus and nutmeg by gas chromatographic, mass, infra-red, and nuclear magnetic spectroscopic techniques.

(4) The elimination of aflatoxin B_1 and its metabolites in the milk and urine of lactating rats, which were given various doses of aflatoxin B_1; and the determination of the effects on the offspring that were allowed to drink contaminated milk.

(5) The study of biliary and urinary metabolites following single intravenous administration of tagged samples of the pesticide synergist,

piperonyl butoxide; myristicin and related congeners from the oil of nutmeg: oil of calamus and its major constituent β-asarone; and isomeric allyl and propenyl derivatives, such as eugenol and isoeugenol.

(6) The assembly of environmental and photochemical apparatus for the elaboration of the effects of ultra-violet radiation, ozone exposure, and temperature on the stabilities of certain groups of pesticides, including the carbamate insecticides, pesticide synergists, herbicides, and other agricultural chemicals.

Publications and Presentations:

1. Chromatography of Ureas, Thioureas and Related Mammalian Metabolites, L. Fishbein, H. L. Falk and P. Kotin, Chromatographic Reviews, Vol. 9, (1968)

2. Chromatography of Methylenedioxyphenyl Compounds. I. Simple and Pesticidal Derivatives, L. Fishbein, H. L. Falk and P. Kotin, Chromotographic Reviews, in press.

3. Chromatography of Methylenedioxyphenyl Compounds. II. Alkaloidal Derivatives, L. Fishbein and H. L. Falk, Chromatographic Reviews, in press.

4. Chromatography of Alkylating Agents. I. Aziridines, Nitrogen and Sulfur Mustards and Derivatives, L. Fishbein and H. L. Falk, Chromatographic Reviews, in press.

5. "Gas Chromatography of Derivatives of Isomeric Chlorophenols and Miscellaneous Herbicides," L. Fishbein and W. L. Zielinski, Jr. Invited paper for Symposium on Pesticidal Derivatives of 155th American Chemical Society Meeting, San Francisco, California, March 31-April 5, 1968.

6. "Relationship of Structure to Sensitivity in Electron Capture Analysis," L. Fishbein and W. L. Zielinski, Jr., 46th Annual Meeting of Virginia Academy of Science, Roanoke, Virginia, May 9-10, 1968.

7. "Cardiac Glycoside Aglycone Interactions with Gas Chromatographic Liquid Phases of Differing Polarity," W. E. Wilson, J. E. Ripley and E. C. Horning, Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Cleveland, Ohio, March 3-8, 1968.

Serial No. DEHS-ASC-001
1. Chemistry Branch
2.
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: "Metabolism of Pesticidal Synergists"

Previous Serial Number: None

Principal Investigator: L. Fishbein, Ph.D.

Other Investigators: J. Fawkes, S. Thompson

Cooperating Units: Pathology Unit, DEHS

Man Years:

Total: 0.4
Professional: 0.2
Other: 0.2

Project Description

Objectives:

Earlier experiments have indicated that methylenedioxpheny pesticidal synergists, such as piperonyl butoxide, in contrast to tropital, were eliminated to some extent in the bile following i.v. administration to the rat. The rate of elimination, although high, did not reach a rapid peak decline but suggested prolonged elimination of the metabolites from the body into the bile. Inhibition of certain detoxification mechanisms and delayed elimination from the body of these chemicals can constitute a hazard by possibly interfering with the induction of enzymatic detoxification of harmful environmental compounds.

Methods Employed:

Thin-layer chromatographic, radioautographic, and liquid scintillation techniques.

Major Findings:

Qualitative and quantitative differences in biliary and urinary metabolites were obtained after the administration of piperonyl butoxide with C^{14} label in the methylenedioxy ring or the side chain.

Evidence for catechol metabolite formation was obtained.

Significance to Bio-medical Research and Programs of the Division

Unequivocal identification of the metabolites of synergistic agents such as piperonyl butoxide would be of value toward the understanding of the mechanisms controlling enzyme detoxification of this class of pesticidal agent.

Proposed Course:

Further separation and elaboration of metabolites of piperonyl butoxide by gas chromatography and gas chromatography-mass spectroscopy, nuclear magnetic resonance, and infra-red spectroscopy; studies to determine whether synergists such as piperonyl butoxide possess enzyme inhibitory activity after absorption from the lung, skin, or gastrointestinal tract.

Serial No. DEHS-ASC-002
1. Chemistry Branch
2.
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: "Aflatoxin and Its Transfer in Milk as an Environmental Hazard"

Previous Serial Number: None

Principal Investigator: H. L. Falk, Ph.D.

Other Investigators: A. Ottolenghi, M.D.

Cooperating Units: Pathology Branch, DEHS

Man Years:

Total: 0.9
Professional: 0.4
Other: 0.5

Project Description

Objectives:

It has been found that lactating animals that have ingested aflatoxin, excrete its metabolites in the milk. To determine, by chromatographic and spectroscopic methods, aflatoxin B_1 and its metabolites in the milk and urine of lactating rats injected with varied doses of aflatoxin B_1. To determine the effects on the offspring that were allowed to drink the contaminated milk. To determine any effect on successive generations.

Methods Employed:

Injecting and milking of rats while under light anesthesia. Chromatography, spectroscopy, and histo-pathology are used in this project.

Major Findings:

The sucklings of lactating rats administered aflatoxin B_1 showed biliary duct proliferation and other pathological changes attributable to aflatoxin damage. There is also some evidence that third generation litters are affected in size and quality.

Significance to Bio-medical Research and the Programs of the Division:

Aflatoxin in contaminated foodstuffs has been established to be an environmental hazard to both man and animals. An understanding of the means and effects of the transfer of this agent from mother to offspring and from animals to humans through milk is of considerable importance.

Proposed Course:

It is expected that this project will come to an end in the next fiscal year.

Serial No. DEHS-ASC-003
1. Chemistry Branch
2.
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: "Metabolism of Myristicin and Congeners"

Previous Serial Number: None

Principal Investigator: L. Fishbein, Ph.D.

Other Investigators: J. Fawkes

Cooperating Units: Pathology, Teratology Units, DEHS

Man Years:

Total: 0.3
Professional: 0.2
Other: 0.1

Project Description

Objectives:

Myristicin metabolism is under study in the rat. Myristicin (5-allyl-1-methoxy-2, 3-methylenedioxy benzene) is of interest for definitive metabolic and stability study due to three recent findings: it has been recently isolated from the oil of nutmeg and is considered, in part, to be responsible for the narcotic effect; it has been isolated from the edible portion of parsnips and found to possess insecticidal and synergistic properties; and it has been isolated from cigarette smoke. (Because commercial American cigarettes contain flavoring additives, including natural oils and resins, it is presumed that myristicin as well as other benzyl esters in smoke are derived from this source rather than tobacco leaf, *per se*).

Methods Employed:

Thin-layer chromatographic techniques for the isolation of biliary and urinary constituents following i.v. administration of myristicin to the rat.

Major Findings:

Identity of metabolites (some of catechol type) is being elaborated.

Significance to Bio-medical Research and the Programs of the Division:

Unequivocal identification of the metabolites and knowledge of the rate of elimination of this environmental agent would be of value in determining whether the exposure to or ingestion of myristicin constitutes a potential hazard.

Proposed Course:

Further separation and elaboration of metabolites of myristicin by gas chromatography and gas chromatography-mass spectroscopy, nuclear magnetic resonance, and infra-red spectroscopy. Study of the metabolism of isomeric congeners such as Croweacin (2-methoxy-1-alkyl-3, 4-methylenedioxy benzene) and cis and trans apiol (2, 5-dimethoxy-1-alkyl-3, 4-methylenedioxy benzene) with a view toward relating isomeric structures to both rates of elimination and qualitative and quantitative nature of bilary and urinary metabolites following single i.v. administration to the rat.

Serial No. DEHS-ASC-004
1. Chemistry Branch
2.
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: "Metabolism of Oil of Calamus and Its Constituents"

Previous Serial Number: None

Principal Investigator: W. E. Wilson, Ph.D.

Other Investigators: L. Fishbein, Ph.D., L. Levy, Ph.D., J. Fawkes

Cooperating Units: Pathology and Teratology Branches, DEHS

Man Years:

Total: 0.5
Professional: 0.4
Other: 0.1

Project Description

Objectives:

Oil of Calamus is an additive that is used in foods, beverages, and drugs. The toxicity of the oil of Calamus (Jammu variety) has been recently reported. Selective metabolic studies are in progress for the elaboration of biliary and urinary metabolites following i.v. adminstration of the intact oil of Calamus (from various sources) in addition to key constituents such as the β-asarone (2, 4, 5-trimethoxy-1-propenyl benzene).

Methods Employed:

Thin-layer chromatography.

Major Findings:

Identification of biliary and urinary metabolites separated by thin-layer chromatographic techniques are in progress.

Significance to Bio-medical Research and the Programs of the Division:

Unequivocal identification of the component(s) of the oil of Calamus responsible for its reported toxicity (as well as the identify of its metabolites) would be of value in determining the extent or the potential hazard of this environmental agent.

Proposed Course:

The constituents of the oil of Calamus can vary, depending on its origin. For example, a source of oil of Calamus (Indian) is reported to consist of cis and trans-asarones, calamene, calamon, camphene, β-pinene, and asaronaldehyde plus a number of unidentified constituents. It is proposed to unequivocally separate and identify the constituents of oil of Calamus from various origins utilizing preparative gas chromatographic and spinning-band fractionation technique for separation and G-C/Mass spectroscopy nuclear magnetic resonance, and infra-red spectroscopy for identification; and to perform selected metabolic and toxicologic studies to further elaborate the specific component(s) responsible for the toxicity of oil of Calamus.

Serial No. DEHS-ASC-005
1. Chemistry Branch
2.
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: "Effect of Environmental Parameters on Pesticidal Stability"

Previous Serial Number: None

Principal Investigator: L. Fishbein, Ph.D.

Other Investigators: Z.L.F. Gaibel, Ph.D.

Cooperating Units: None

Man Years:

Total: 0.2
Professional: 0.2
Other: 0

Project Description

Objectives:

Different classes of pesticidal agents have been known to possess varying stabilities when exposed to environmental effects in the field. The exposure of a number of classes of pesticidal agents such as carbamates, ureas, aziridine, methylenedioxyphenyl compounds, and hydrazides (representative of herbicides, fungicides, chemosterilants, etc.) in an environmental chamber permitting the monitoring of ultra violet, ozone, varying humidities, and thermal parameters would permit a kinetic evaluation of degradation and a more facile collection of degradation products.

Methods Employed:

Environmental exposure chamber, ozonolysis, and photochemical vessels for exposure of pesticidal derivatives.

Major Findings:

None to date; equipment being installed and evaluated.

Significance to Bio-medical Research and the Programs of the Division:

Identification of the degradation products of these agents under various field conditions would aid in the identification of any potential hazardous agent that may be produced under environmental conditions.

Proposed Course:

Refine techniques for the elaboration of the environmental effects on pesticide stability. Identify degradation products of the broad spectrum of pesticidal agents and where degradation products suggest a potential hazard, synthesize or obtain requisite amounts of the material for future acute and chronic feeding and metabolic studies.

Serial No. DEHS-ASC-006
1. Chemistry Branch
2.
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: "Development of Analytical Methodology"

Previous Serial Number: None

Principal Investigator: L. Fishbein, Ph.D.

Other Investigators: W. E. Wilson, Ph.D. and J. Fawkes

Cooperating Units: None

Man Years:

Total: 0.4
Professional: 0.3
Other: 0.1

Project Description

Objectives:

The development of new and improvement of approved analytical techniques is an integral requirement for the efficacious elaboration of diverse studies in the Chemistry Branch, e.g., metabolic and stability studies DEHS -001 through -005. The development of analytical methodology programs include: (a) study of the thin-layer chromatographic (TLC) behavior of the isomeric allyl, propenyl, and dihydro derivatives related to the components of the oil of calamus and oil of nutmeg; (b) the TLC analysis of the pesticidal isomeric chlorophenols via their respective isomeric fluorosulfonyl benzene chlorophenyl sulfonates; (c) the gas chromatographic analysis of the chemosterilants Tepa and Thio-tepa from mammalian blood, and (d) gas chromatographic analysis of the aflatoxins by pyrolytic and/or derivative techniques.

Methods Employed:

Thin-layer chromatography and gas chromatography (flame ionization, electron-capture, and thermal conductivity).

Major Findings:

(1) TLC procedures have been developed using silver nitrate and silanized plates for the separation and identification of diverse isomeric derivatives (allyl, propenyl, and dihydro) related to components of the oils of nutmeg, parsley, and calamus.

(2) The synthesis and TLC separation of the isomeric mono chlorophenols via their respective isomeric fluorosulfonyl benzene chlorophenyl sulfonates has been achieved.

Significance to Bio-medical Research and the Programs of the Division:

Successful development of the analytical methodology in the areas delineated above will accelerate the successful conclusion of a number of metabolic and degradation studies in progress in the Chemistry Branch as well as be of utility for studies involving chemosterilants in the Animal Science and Technology Branch and Cell Biology Branch.

Proposed Course:

Continuation of effort utilizing diverse gas chromatographic procedures for the analysis of aflatoxins which would permit greatly enhanced separation and detection of the aflatoxins and their metabolic products from diverse tissues.

Serial No. DEHS-ASC-007
1. Chemistry Branch
2.
3. Research Triangle Park, N.C.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: "Synthesis of Derivatives for Metabolic and Teratogenic Investigations"

Previous Serial Number: None

Principal Investigator: L. A. Levy, Ph.D.

Other Investigators: None

Cooperating Units: Teratology DEHS

Man Years:

Total: 0.5
Professional: 0.5
Other: 0.0

Project Description

Objectives:

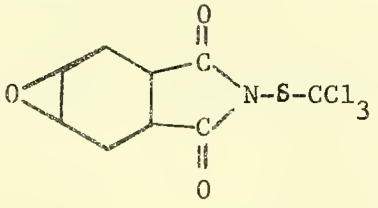
The Synthesis of a variety of intermediates and congeners which are required for both metabolic and teratogenic investigations.

Methods Employed:

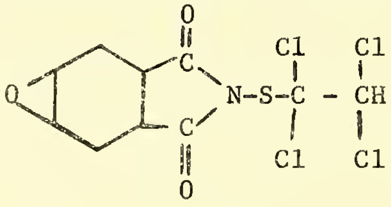
Diverse synthetic and isolation techniques.

Major Findings:

(1) The epoxides of the fungicidal agents Captan {N-trichloromethyl thio-4-cyclohexene-1, 2-dicarboximide} (I) and Difolatan {N-1, 1, 2, 2-tetrachloroethyl mercapto-4-cyclohexene-1, 2-dicarboximide} (II) were prepared.



(I)



(II)

(2) Elemicin (1-allyl-3, 4, 5-trimethoxy benzene) and isoelemicin (1-propenyl-3, 4, 5-trimethoxy benzene) were prepared, the latter via the Wittig reaction with 3, 4, 5-trimethoxy benzaldehyde and ethyl triphenyl phosphonium bromide. The general applicability of this reaction is being investigated for the preparation of other required intermediates. For example, use of 2, 4, 5-trimethoxy benzaldehyde would yield asarone.

Significance to Bio-medical Research and the Programs of the Division:

(1) The preparation of the epoxides of Captan and Difolatan permits the possibility of investigating their metabolism and teratogenicity *per se* and also permits the more elaborate investigation of the metabolism of Captan and Folpet. The possibility exists that these fungicides may be metabolized *in vivo* in an analogous manner to aldrin and heptachlor.

(2) The preparation of elemicin and isoelemicin permits more definitive metabolic studies of components related to constituents of the oils of Calamus and nutmeg.

Proposed Course:

Continuation of synthetic chemistry efforts to furnish materials in required quantity and purity for metabolic and degradation studies.

Summary Statement
Office of Associate Director for Scientific Information
July 1, 1967 - June 30, 1968

Scientific Liaison with Categorical Environmental Health Programs

Purpose is to maintain mutual awareness of relevant scientific and technical activities between the intramural operations of DEHS and the categorical environmental health programs in other parts of DHEW. Complete understanding and excellent working relationships have been established during the year with the Bureau of Disease Prevention and Environmental Control, and relationships are developing at the component Center levels. Relevant Project Plans have been received from the Bureau components, and progress reports have been requested. DEHS projects, to date, have been insufficiently formulated to permit reciprocation. A Program Liaison Officer spends about 40 percent of his time visiting the categorical programs and maintaining close communication. Interchange of visits by administrative and scientific personnel has taken place. Regular document exchange is being developed.

Quick Retrieval System for Scientific Information

Objective is the development and operation of a system for quick retrieval of information on scientific topics relevant to the DEHS program. The selected system involves: (a) selection of most relevant items from incoming information; (b) analysis of items for key content; (c) preparation of aperture cards containing microform of item, minimum typescript, and punching of key words; (d) serial storage of original items; (e) filing of aperture cards in a macro and/or micro index system; (f) manual retrieval of cards by indexed terms; (g) immediate printing of desired microform. So far, only unpublished documentary information has been entered into the system. The key punching permits later conversion to an automated system.

Intramural Scientific Information Services

A limited Library facility has been set up in the Center to receive some 150 periodicals and 1,000 books, for a 5-10 year holding period. Wider coverage is provided by a good exchange and facsimile service offered by the three neighboring university and other technical libraries. Recourse is available to both the NIH Library and the National Library of Medicine. Additional external service arrangements are under consideration.

In addition to the normal library services, a start has been made toward a personal user service to intramural scientists, by which incoming items are brought to the attention of research personnel, searches are facilitated, and external sources of scientific information tapped as required.

Scientific Information Evaluation and Reporting Service

The general outlines of an intramural service have been developed which, when operative, will: (a) permit a review of the wide range of environmental stressor patterns, with evaluation of both the significance for man and the current state of understanding; (b) facilitate the preparation of position papers on topics of national interest; and (c) arrange for the preparation of authoritative reviews of environmental health topics of particular import.

SUMMARY REPORT
OCCUPATIONAL STUDIES UNIT
July 1, 1967 - June 30, 1968

The program of the Occupational Studies Unit during the past year has, in the main, consisted of the continuation and completion of several studies transferred from the National Cancer Institute when the Unit was formed in July 1967. Extension of the program into other areas has been delayed by the need for total commitment to the ongoing studies of occupational carcinogenesis and problems encountered in recruiting sufficient scientific and supporting staff.

The major in-house activities during the year were centered around 1) the up-dating and analysis of Uranium Miner data leading to the preparation of a report to the Federal Radiation Council (May 15, 1968) to be used in a review of the adequacy of current standards for radiation exposures in mines, and 2) the tabulation and analysis of Religious Orders findings undertaken in collaboration with the National Cancer Institute. Other activities concerned with specific studies included assessment of Steelworker findings through 1961 and the preparation of several manuscripts; up-dating of mortality findings on chromate workers; and overseeing contracts with Wayne State University and the University of Pittsburgh.

Due to the limited size of the professional staff in relation to the program, almost all of the effort during the past year has been directed to specific research projects. In spite of this limitation, the staff has been able to make significant contributions to general programs of the Division and the NIH. Activities included in this area were the following:

1. General planning and direction of scientific program of the Unit.
2. Recruitment and development of professional staff.
3. Service as members of scientific committees, as consultants to special research groups, and as faculty members of academic institutions.
4. Effecting liaison with and obtaining cooperation of local, state, and Federal agencies for our follow-up program.

Recruitment of qualified epidemiologists and biostatisticians, even at the junior level, remains a problem. During the year we were successful in recruiting an EDP programmer with formal training in mathematics and a staff nosologist trained at the National Center for Health Statistics.

Dr. Lundin has served during the past year as a member of three research committees, as a consultant to the Occupational Health Program studies of asbestos exposures, and as a faculty member at two universities. Dr. Lloyd serves as faculty member at one university. Mr. Rush is a Research Assistant at the University of Pittsburgh, Graduate School of Public Health, and Mrs. Winifred M. Mendez is Nurse Epidemiologist for the Cutting Oil study at Wayne State University and continues as consultant to the Uterine Cancer Morbidity - Cytology Study at the University of Louisville. Dr. Lloyd, Dr. Lundin, and Mr. Rush have significantly expanded our follow-up program by enlisting or enhancing the collaboration of various agencies. During the year, arrangements were made with the Social Security Administration for a general agreement covering all of our occupational studies, and discussions regarding use of national IRS records were initiated. Mr. Rush has obtained the cooperation of welfare and unemployment agencies in the Western Pennsylvania area for the follow-up of Allegheny County Steelworkers; Dr. Lloyd has made arrangements with Canadian authorities for follow-up of steelworkers through their unemployment records; and Dr. Lundin has enlisted the cooperation of the Foreign Quarantine Division for locating death information on persons dying outside the United States.

Special Activities

J. William Lloyd, Sc.D.

- a) Faculty member, Clinical Assistant Professor of Community Medicine and International Health, Georgetown University School of Medicine.
- b) Invited to prepare examination questions, in the Field of Community Health and Community Medicine by the Professional Examination Service, American Public Health Association.

Frank E. Lundin, Jr., M.D.

- a) Member Etiology Contract Review Committee, NCI, Etiology Area (Until its termination in the fall of 1967).
- b) Member Inter-service Committee on Asbestos Research.
- c) Member Technical Advisory Committee on Uranium Miners Study.
- d) Consultant, Epidemiologic Study of Asbestos Products Industry, Occupational Health Program, NCUIH, BDPEC, Cincinnati, Ohio.
- e) Faculty member, Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health.
- f) Faculty member, Clinical Assistant Professor of Community Medicine and International Health, Georgetown University School of Medicine.

H. W. Rush

Member and PHS Representative of Greater Pittsburgh Federal Executive Association.

M. F. Heid

Invited to participate in the preparation of the 8th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death, WHO, Geneva.

Serial No. DEHS-E-01
(NCI-4253)
1. Epidemiology Branch, OASDD
2. Occupational Studies Unit
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Mortality Among Steelworkers

Previous Serial Number: NCI-4349

Principal Investigator: J. William Lloyd, Sc.D.

Other Investigators: F. E. Lundin, Jr., M.D.; and A. Ciocco, Sc.D.

Cooperating Units: National Cancer Institute, Graduate School of Public Health, University of Pittsburgh, and the American Iron and Steel Institute

Man Years:

Total: 3.5
Professional 1.5
Other: 2.0

Project Description

Objectives:

1. a) To determine which excesses and deficits in cause-specific mortality are associated with particular occupational subgroups in the steel industry and how this might be related to length of exposure.

   b) To determine the interrelationships among other variables, not necessarily related to occupational exposures, which have been previously associated with differential risks for specified causes of death.

2. To develop methodological techniques for the conduct of long-term occupational studies and to develop mathematical models for assessment of latent effects and risk associated with particular occupational exposures at specified intervals and at various ages.

Methods Employeed:

A study is being made of the mortality experience of approximately 59,000 steelworkers employed by three major firms in Allegheny County, Pennsylvania, in 1953. Occupational histories and pertinent demographic information have been abstracted from employment records of the three firms. The vital status of each employee through 1961 has been determined by follow-up through Social Security records, postal inquiry, search of city directories, and reference to records of other governmental agencies. Extension of follow-up through 1966 was initiated during the last year.

A study of coke-oven worker mortality is being made through the cooperation of twelve steel plants distributed throughout the United States and Canada. Employment records are collected on all men employed at the coke ovens between 1951 and 1955, and a two-for-one control group of other steelworkers matched for race and date of initial employment. Determination of vital status through 1966 is made by reference to Social Security records and other appropriate follow-up procedures.

Collaboration on the collection and analysis of steelworker and coke-oven worker data is provided by the University of Pittsburgh Department of Biostatistics under contract with the National Cancer Institute (PH43-62-147) and the American Iron and Steel Institute.

Major Findings:

Analysis of Allegheny County data through December 1961 showed that nonwhite coke-oven workers employed at the "topside" of the ovens had experienced lung cancer mortality markedly in excess of that predicted by the mortality rates for other nonwhite steelworkers (14 observed vs. 2.2 expected). The level of risk for white "topside" workers could not be determined because of the small number of white men employed in that area. The mortality experience of men employed at other areas of the coke-ovens was also suggestive of a possible lung cancer excess for white (8 observed vs. 5.3 expected) and nonwhite (9 observed vs. 5.9 expected) employees.

The finding of such a striking mortality differential in the nonwhite "topside" workers could not be explained by any bias in selection or differences in demographic characteristics of coke-oven workers and other steelworkers in Allegheny County. On the other hand, an earlier unpublished study of U.S. coke-oven workers showed a lung cancer excess limited to nonwhite workers in Allegheny County.

A number of other occupational groups within the steel industry may have experienced higher than expected mortality; but because the number of years at risk through 1961 for men employed in these occupations was too small to allow for a firm conclusion of excess risk, the study period was extended through 1966.

Significance to Bio-medical Research and the Program of the Division:

These studies will provide information regarding the pathogenesis and epidemiology of cancer and other chronic disease as related to certain occupational exposures. They are also of great value in developing methodologies for field studies of chronic illness consequent to exposure in the occupational environment.

Proposed Course of Project:

Work histories for the Allegheny County study population have been updated, and follow-up to determine vital status through 1966 continues. Records of coke-oven workers and controls have been collected from ten plants cooperating in the Non-Allegheny County phase of the study. Records from two of the twelve plants initially contacted by the American Iron and Steel Institute, proved inadequate for our purposes. Follow-up of steelworker and coke-oven workers populations have been delayed by the heavy work load at the Social Security Administration. Consequently, original deadlines will have to be extended. A report of steelworker mortality experience through 1966 should be completed about January 1, 1969, and a report on the coke-oven worker experience shortly thereafter. Several manuscripts covering the methodological problems of industrial population study and the lung cancer experience of coke-oven workers through 1961 are being prepared.

Serial No. DEHS-E-02
(NCI-4338)
1. Epidemiology Branch, OASDD
2. Occupational Studies Unit
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Cancer Mortality Among Catholic Brothers and Sisters in Several Teaching Orders in the United States

Previous Serial Number: NCI-4338

Principal Investigator: J. F. Fraumeni, Jr., M.D. (NCI)

Other Investigators: J. W. Lloyd, Sc.D.; E. M. Smith, M.Sc.; J. K. Wagoner, M.S. (NCI); F. C. Madigan, S. J.

Cooperating Units: National Cancer Institute; Social Science Research Institute, Xavier University, Philippines

Man Years:

Total: 3.2
Professional: 1.2
Other: 2.0

Project Description

Objectives:

1. To determine cause-specific mortality in certain Catholic teaching orders with particular reference to cancer.

2. To compare the cause-specific mortality of Catholic teaching orders with the corresponding risk in the general population and to determine whether significant excesses or deficits exist.

Methods Employed:

1. Information on approximately 70,000 individuals comprising 62 Catholic religious communities from 1900-1954 had been gathered, coded, and analyzed in a previous study carried out by Father Madigan at the Institute for Research and Social Science, University of North Carolina. Although deaths were recorded, no attempt was made to determine the underlying cause.

2. For comparison of mortality with Brothers and Sisters, the U.S. white population was selected. Because causes of death by sex, race, and age were not available for the U.S. as a whole prior to 1914, data for Massachusetts were used for the earlier years. The number of deaths by cause for the U.S. white population from 1914 through 1954,in addition to the Massachusetts deaths,were punched on IBM cards. The causes of death were then reclassified on magnetic tape according to the 6th Revision of the International Classification of Causes of Death using electronic data processing systems.

3. Tabulation and biometric analysis is being made of the mortality data to discover similarities to and differences from similar data relative to the general population.

Major Findings:

A published paper has described the marked excess of breast-cancer mortality in nuns, stressing the occurrence of a "break" in the age curve at menopause. The phenomenon appears to have a biological basis and to be related particularly to the unmarried state. Preliminary data for nuns show a deficiency of uterine cancer and excesses in ovarian and digestive cancers.

Significance to Bio-medical Research and the Program of the Division:

This study, which is much larger in scope than an earlier one undertaken by the NCI, (J.N.C.I., vol. 12, no. 6, 1959), should help to clarify some fragmentary evidence that the incidence of certain forms of cancer is different in some religious orders than in the general population. These differences may be due to variations in the way of life or to sexual, reproductive, or hormonal differences associated with the marital state. Investigation of underlying cause differentials observed in the populations compared may advance the understanding of the genesis of cancer.

Proposed Course of Project:

Analysis of the Sisterhood data is nearly completed. A manuscript describing the site-specific cancer experience is being prepared.

Serial No. DEHS-E-03
1. Epidemiology Branch, OASDD
2. Occupational Studies Unit
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Epidemiological Study of Lung Cancer in Workers Exposed to the Inhalation of Zinc Chromate Paint in Airplane Construction and Maintenance Plants.

Previous Serial Number: NCI-4200 (Calendar Year 1961)

Principal Investigator: W. W. Payne, Sc.D.

Other Investigators: J. W. Lloyd, Sc.D.; E. M. Smith, M.Sc.

Man Years:

Total: 1.1
Professional: 0.1
Other: 1.0

Project Description

Objectives:

Epidemiological studies have shown that workers in chromate-producing plants have an abnormally high incidence of cancer of the lung. Observations in Europe suggest that workers exposed to chromium pigment also experience a respiratory cancer hazard, but epidemiological evidence is lacking.

The airplane manufacturing and maintenance industry appears to offer the best opportunity for studying workers who have been exposed to the inhalation of zinc chromate paints and related compounds. This follow-up study of persons who have been engaged in work in which there is an exposure to chromium compounds was designed to determine whether exposure to zinc chromate paint by inhalation results in an increased risk to lung cancer.

Methods Employed:

Arrangements were made with the U.S. Air Force to obtain the names of painters, whose employment had been terminated during the ten year period prior to July 1959, together with identifying information and a brief summary of each worker's employment at the base. For controls, similar data were obtained for workers in the same plants who were presumably not exposed to chromium. Date of birth, sex, and length of employment were matched as closely as possible.

From the Social Security Administration or Federal retirement records, it was learned whether a death claim had been filed for each of these workers and, if so, in which state. Using the available information, copies of death certificates were obtained from the several State Health Departments. Where any form of cancer or any pulmonary disease was specified as the cause of death, additional information on the diagnosis was requested from the attending physician. For each worker whose death certificate was obtained, a complete employment history was obtained from Civil Service Records. Frequently information was available regarding exposures, type of work, injuries, and illness.

Similar information was obtained from a private airplane manufacturing company for both painters and a control group, but detailed employment history was not available in a form that could be used readily.

Unfortunately no smoking history was available for these workers, but there is no reason to suspect that smoking habits for the group would be different from those of the controls, especially in view of strict on-the-job smoking regulations.

Major Findings:

The preliminary results for the two Air Force bases are summarized in the table below. Electricians and sheet metal workers are the two groups of controls. No findings for the private manufacturing plant are given, because the number of deceased painters was too small.

Number of Deaths and Proportionate Distribution by Cause
Chromate Painters and Controls 1950-1960

	Painters		Controls	
	Number	%	Number	%
All Causes	84	100.0	147	100.0
Total Malignant Neoplasms	25	29.8	23	15.6
Digestive Organs	7	8.3	9	6.1
Respiratory System	7	8.3	5	3.4
Genito-urinary Organs	4	4.8	3	2.0
Brain and CNS	2	2.4	0	0.0
Leukemia and Lymphoma	3	3.6	2	1.4
Other Sites	2	2.4	4	2.7

Significance to Bio-medical Research and the Program of the Division:

The number of workers for whom death records were found in the original follow-up is too small to be conclusive, but it appears that a further follow-up at this time is warranted.

Proposed Course of Project:

IBM cards have been punched and are being sent to the Social Security Administration to determine how many additional deaths have occurred since the last follow-up in 1961. After analysis of the additional deaths, if the findings warrant, the study will be enlarged to afford a complete examination of work histories for both the study and the control populations.

Serial No. DEHS-E-04
1. Epidemiology Branch, OASDD
2. Occupational Studies Unit
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Epidemiologic Studies of Occupational Exposure to Cutting Oil Mists*

Previous Serial Number: None

Principal Investigator: F. E. Lundin, Jr., M.D.

Other Investigators: T. L. Nghiem, M.D.; W. M. Mendez, R.N., B.S.; and A. J. Vorwald, M.D.

Cooperating Units: Wayne State University, Detroit, Michigan

Man Years:

Total: 1.2
Professional: 1.1
Other: 0.1

Project Description

Objectives:

To determine whether occupational exposure to cutting oil mists produces significant disease of the respiratory tract. In particular, evidence of impaired pulmonary function, chronic bronchitis, obstructive emphysema, chronic pneumonitis, pulmonary fibrosis, other distinctive pathologic changes, and respiratory cancer is sought.

Methods Employed:

1. A mortality study is made of approximately 8,000 subjects whose employment (for one or more years between 1937 and 1966) exposed them to cutting oil mists. Length, time, and relative intensity of exposure to cutting oil mists is determined from employment records. Death certificates are located through retirement and insurance records and the Social Security Administration. Using a life table technique, person years at risk by age, race, and

---

*This study is primarily financed by contract PH43-66-53 currently in Etiology, NCI.

year are determined. The cause-specific mortality of the study group, classified by degree of exposure to cutting oil mists, is compared with that for blue collar workers who were not significantly exposed to cutting oil mists and to mortality for the general population of the area.

2. Approximately 1,000 employees currently exposed to cutting oil mists and an equal number of control subjects complete questionnaires which include smoking and occupational histories, and have chest x-rays, pulmonary function tests, and complete medical histories and physical examinations. (The participating industry provides the medical personnel for this aspect of the study.)

3. A final subgroup of approximately 2,000 workers who left employment after January 1, 1956, are compared with a group of unexposed employees with regard to abnormalities of their chest x-rays and selected diseases requiring hospitalization.

Major Findings: None

Significance to Bio-medical Research and the Program of the Division:

Carcinogenic hazards for man can be identified by epidemiologic studies of the effects of selected occupational exposures. In this way preventive measures will be undertaken. This study heralds a program of epidemiologic studies which will be initiated provided the following conditions obtain: 1) experimental evidence of carcinogenic activity, 2) large numbers of employees exposed over a period of years, and 3) collaboration between NIH, industry, and possibly, academic institutions.

Proposed Course of Project:

As originally planned the study was to require 3 to 5 years for completion. However, a one-year delay in recruiting an epidemiologist, his loss through death one year ago, and the more recent loss of time through disability of the Project Director may require additional time for completion of the study. Assistance from personnel of the Occupational Studies Unit will continue to be required for processing and analysis of data. This requires assignment of the Nurse Epidemiologist to Wayne State University.

Serial No. DEHS-E-05
1. Epidemiology Branch, OASDD
2. Occupational Studies Unit
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Health Hazards of Uranium Miners of the Colorado Plateau

Previous Serial Number: NCI-4335

Principal Investigator: F. E. Lundin, Jr., M.D.

Other Investigators: V. E. Archer, M.D.; J. W. Lloyd, Sc.D.; J. K. Wagoner, M.S.; E. M. Smith, M.Sc.; and D. A. Holaday, M.A.

Cooperating Units: Salt Lake City Field Station, Occupational Health Program, NCUIH, BDPEC, PHS

Man Years:
Total: 4.5
Professional: 1.5
Other: 3.0

Project Description

Objectives:

1. To study the cause-specific mortality experience of underground uranium miners in relation to standard medical examination findings, cigarette smoking, and airborne radiation exposure data.

2. To determine the quantitative relationship between airborne radiation exposure and the incidence of respiratory cancer.

3. To delineate the role of a number of factors which might influence carcinogenic response to airborne radiation.

4. To develop realistic models for relating environmental exposure to cancer and other chronic diseases.

Methods Employed:

1. Study is made of miners and millers of the Colorado Plateau area who volunteered for at least one physical examination and provided social and occupational data in sufficient detail to permit follow-up study of their health status. (Physical examinations were performed in 1950, 1951, 1953, 1954, 1957, and 1960.)

2. For the past several years, sputum collected annually from actively employed uranium miners has been examined cytologically.

3. Follow-up study is maintained through an annual census of the uranium mining industry and by the collection of information of individuals by direct mail and other methods. Deaths are ascertained by review of all local newspapers in the area and through the records of the Social Security Administration. Death certificates are obtained for known decedents and are classified as to cause of death by our nosologist.

4. Medical information from autopsy, hospital, and physician reports is obtained, and histopathologic studies of both malignant and non-malignant tissues are made.

5. Approximately 12,000 radon-daughter exposure measurements were made during the course of the program. These are used for quantitating the carcinogenic response to radiation.

Major Findings:

A study of mortality experience among 3,415 white, underground uranium miners during the period 1950 through June 1965 has shown an excessive occurrence of respiratory tract cancer (37 deaths observed as compared with 7.3 expected).

Study of the quantitative relationship between airborne radiation and respiratory cancer shows that age-standardized incidence tends to increase progressively from the lowest cumulative exposure category to the highest. The dose-response relationship persists when confounding variables are taken into account, among them being time since onset of exposure as well as cigarette consumption.

The carcinogenic effect of airborne radiation is specific for the respiratory tract.

The pathology of respiratory cancer in uranium miners is unlike that observed among an age-smoking-residence matched control group while being similar to that observed among factory workers exposed to a radiomimetic agent, mustard gas.

Mortality from respiratory tract malignancy increased from a 4-fold excess in an earlier analysis to a 9-fold excess for the succeeding 18-month period. A relatively greater excess occurred after the age of 45 years; only 35 of 37 lung cancer deaths occurred among one-third of the person-years in the study. This age effect could not be explained by amount of radiation exposure and number of years after onset of underground uranium mining.

The great excess of lung cancer among U.S. uranium miners is largely limited to cigarette smokers. However, data are insufficient to determine whether non-cigarette smokers also have an increased risk.

Significance to Bio-medical Research and Programs of the Division:

The findings of the present quantitative study emphasize the value of developing analytical methods which utilize retrospective work histories and exposure data to identify and study an etiologic agent in environmental carcinogenesis. These data may also establish the role of the following factors: age at first exposure, latency, antecedent respiratory disease, tobacco consumption, and radiation dosage. Such knowledge will be of value in two ways: 1) To improve our understanding of the mechanisms of carcinogenesis in man. 2) To form the basis for standards of airborne radiation in mines (See FRC Report #8 - Preliminary and Revised) and possibly 3) to suggest means of controlling the health hazards of uranium mining in addition to limitation of exposures.

Proposed Course:

Of particular interest is the lowest radiation exposure associated with increased lung cancer risk and the relationship between cigarette smoking and radiation-induced cancer. A dose-response analysis of radiation and lung cancer-cell type is being carried out. More sophisticated models are being developed to delineate the interrelationships among a number of factors which might influence carcinogenic response. Mortality data will continue to be analyzed at intervals to determine the true slope and placement of the dose-response relationship.

Currently, a report of an analysis of mortality during the period 1950 through September 1967 is being prepared for the Federal Radiation Council.

Recently, the Occupational Studies Unit was given responsibility for study of all uranium miners who have been enumerated in annual censuses of the uranium industry. If this includes study of sputum cytology, the following course is proposed during the next 18 months;

1) Develop a computer-based data linkage and retrieval system.

2) Put all existing uranium-miner data into this system.

3) Determine mortality experience of all uranium miners known from past mine censuses which commenced in 1955.

4) Analyze sputum-cytology readings in relation to radiation exposure and smoking and subsequent lung cancer diagnosis and mortality.

5) Determine the need for obtaining employment histories of uranium miners known only from censuses.

6) Do feasibility studies of ways to obtain such employment histories.

7) Do feasibility studies, primarily under contract, of ways to measure body burdens of lead 210.

8) Develop means to relate body burden of lead 210 to original exposures.

One would anticipate that a combination of employment histories, mine radiation estimates,and measurement of body burdens of lead 210 would give the best estimates of dose to the respiratory tract.

Publications and Presentations:

1. Archer, V. E. and Lundin, F. E. Jr.: Radiogenic Lung Cancer in Man; Exposure-Effect Relationship. Environmental Research. 1:370-383, 1963. (In press)

2. "Lung Cancer among U.S. Uranium Miners: Current Assessment of Risk",Frank E. Lundin, Jr., M.D. Paper presented to the Epidemiology Exchange of American Public Health Association, October 24, 1967, Miami, Florida. Co-authors were Victor E. Archer, M.D.; Elizabeth M. Smith, M.Sc.; and Joseph K. Wagoner, M.S.

3. Dr. Lundin participated in Federal Radiation Council Uranium Miners Task Group meetings on April 22, 1967; September 5, 1967; March 7, 1968; and May 29, 1968.

Serial No. DEHS-E-06
1. Epidemiology Branch, OASDD
2. Occupational Studies Unit
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Study of the Cancer Experience of Non-uranium Hard Rock Miners in the Rocky Mountain Area

Previous Serial Number: NCI-4334

Principal Investigator: F. E. Lundin, Jr., M.D.

Other Investigators: J. W. Lloyd, Sc.D.; E. M. Smith, M.Sc.

Cooperating Units: Certain mining companies and the Salt Lake Field Station, Occupational Health Program

Man Years:

Total: 0.6
Professional: 0.1
Other: 0.5

Project Description

Objectives:

1. To delineate the factor(s) responsible for the excess cancer mortality previously reported among long-term metal miners.

2. To determine the quantitative relationship between cancer and degree of exposure as measured by the length of underground employment and ventilation practices.

3. To study cancer mortality among metal miners with regard to the interaction of

    a) age at first exposure

    b) changing ventilation

    c) latency

    d) dosage

4. To develop retrospective methods for use in future studies of occupational carcinogenesis.

Methods Employed:

1. Company records of 120,000 metal miners were reviewed and the occupational, medical, and vital statistics data were abstracted for 16,000 men who worked for the industry in 1937 or later, with initial employment prior to 1954, and with one or more years of underground service.
2. Deaths and reported disability are ascertained by review of company files and through records of claims from Social Security Administration.
3. Death certificates are obtained from State health departments and classified by the staff nosologist.
4. The modified life table method will be used to compare the miners' cancer mortality experience by age at first exposure, latency, dosage, ventilation standards, calendar year, and age with comparable rates for white males living in the same area.

Major Findings:

Life table analysis has shown an excessive occurrence of pulmonary diseases, both neoplastic and infectious, and of heart disease among long-term metal miners. The excess of respiratory tract cancer (47 deaths observed as compared with 16.1 expected) was not attributed to age, smoking, nativity, urbanization, heredity, socioeconomic status, diagnostic accuracy, or silicosis.

Significance to Bio-medical Research and the Program of the Division:

The finding of differential respiratory cancer risk for miners with specific ore exposures may help identify an environmental carcinogen under field conditions. These extensive data may also establish whether the factors of age-at-first-exposure, latency, cessation of exposure, and dosage act in a manner comparable to carcinogenesis experiments. Intense interest in the results of this study has developed because low levels of airborne radiation are present in the mines. While radiation may not be the only carcinogen involved, it is unlikely that any greater risk of lung cancer can be attributed to the amount of radiation exposure in these mines.

Proposed Course of Project:

Little effort is given to this project at present because of the limited staff available for processing the large volume of records. When additional staff is recruited, mortality and disability claims data will be obtained from the Social Security Administration and death certificates will be obtained and the causes of death coded. Employment histories will be coded concurrently. Models are being developed to delineate the interrelationships among a number of factors which might influence the carcinogenic response to metal mining exposures.

DIVISION OF RESEARCH SERVICES

Report of Program Activities
July 1, 1967, through June 30, 1968

CONTENTS

Page

Division of Research Services---------------------------------- 1

Research Facilities Planning Branch---------------------------- 7

Plant Engineering Branch--------------------------------------- 21

Laboratory Aids Branch--- 39
Individual Project Reports
1. Chronic Murine Pneumonia of the Albino Rat--------------- 51
2. Focal Necrosis of the Liver of Rabbits------------------ 52
3. Febrile Hemorrhagic Disease of Monkeys------------------ 53
4. Canine Blood Donors------------------------------------- 55
5. The Effects of a Hematinic on the Blood Picture of Donor Dogs--- 57
6. Canine Hemolytic Anemia--------------------------------- 58
7. Hematologic and Bacteriologic Characteristics of Stored Canine Blood------------------------------------ 59
8. Feed Consumption Studies in the Canine------------------ 61

Environmental Services Branch---------------------------------- 63

Biomedical Engineering and Instrumentation Branch-------------- 73
Individual Project Reports
1. Mathematical Analysis of Pharmacokinetics - Cancer Chemotherapy--- 88
2. Mathematical Analysis of Pharmacokinetics - Effect of Artificial Kidney-- 89
3. Segmented Polyurethane--------------------------------- 91
4. Myocardial Infarction Research Unit Instrumentation and Data Acquisition Systems---------------------------- 93
5. Rat Identification System------------------------------ 94
6. Artificial Heart Assist System------------------------- 95
7. Automated Serological Scanner System------------------- 96
8. Physical Correlates of Animal Colony Behavior---------- 97
9. Automated Amino Acid Analysis-------------------------- 98
10. Automated Sample Combustion System-------------------- 99
11. Utility of Lasers in Biological Research and Clinical Applications--100

Library Branch---103

Medical Arts and Photography Branch----------------------------109

NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Report of Program Activities
July 1, 1967, through June 30, 1968

A. Objectives

The objective of this Division is to provide scientific, technical, and engineering services to support and further the research programs of the National Institutes of Health. Since all of these services are geared to the needs of the Institute programs, the Division makes a continuous effort to keep informed of Institute plans. The Division's organization, staffing, and functions are adjusted accordingly to maintain an effective program of centralized services.

B. Current Programs

The Division of Research Services comprises some 1,300 persons with almost 200 individual occupational skills and is composed of an Office of the Director and seven branches: Biomedical Engineering and Instrumentation, Environmental Services, Laboratory Aids, Library, Medical Arts and Photography, Plant Engineering, and Research Facilities Planning.

The programs of the Division can be divided into two broad classifications:

1. Programs in direct support of research

    a. Design, development, and fabrication of instruments and materials
    b. Biomedical engineering of methods and systems
    c. Production of bacteriologic and tissue culture media
    d. Preparation of sterile glassware
    e. Production of genetically defined rodents and rabbits
    f. Quarantine and conditioning of dogs, cats, and primates
    g. Maintenance of farm animals
    h. Animal surgery and recovery
    i. Animal health services
    j. Still and motion picture photography
    k. Graphic arts services and exhibits design
    l. Medical illustration and model making
    m. Library services
    n. Foreign language translation

2. Programs related to NIH facilities and proper environment

    a. Engineering liaison in the design and construction of new NIH facilities
    b. Development of improved facilities and equipment

c. Operation, maintenance, and repair of NIH physical facilities
d. Professional engineering and craft services for alterations, improvements, and installations
e. Maintenance of NIH grounds
f. Environmental services designed to maintain and improve the health of NIH patients and employees

C. Program Progress and Accomplishments

During FY 1968 the Office of the Director sought to strengthen management of DRS activities by realigning functions within and among several of the branches.

The most extensive area of reorganization concerns the Research Facilities Planning Branch and the Plant Engineering Branch. In order to handle NIH's increased construction and maintenance workloads, RFPB was divided into an Engineering Design Branch and a Construction Engineering Branch. At the same time, the engineering design and construction activities of PEB were transferred into the appropriate new branch, with PEB retaining responsibility for operation, maintenance, and alterations of the NIH buildings and grounds. The reorganization was approved and is scheduled to be implemented early in FY 1969.

In another change, the sectional structure of the Environmental Services Branch was reorganized to enable the branch to be more responsive to Institute needs. The branch organization is now based on functional programs rather than professional disciplines, and recognizes the growing role of biohazards control as a prime factory in maintaining a satisfactory environment.

The Division will continue to examine its functions throughout FY 1969. Changes in I/D programs will be evaluated in terms of possible impact on our service areas. Where realignment, elimination, or addition of new functions is indicated, appropriate reorganizations will be implemented.

The successful recruitment of a Chief for the Medical Arts and Photography Branch further strengthened Division efforts to provide the most effective supporting services to Institute programs.

Workload Measurement

Installation and refinement of the workload measurement and management reporting systems continues to occupy a position of high priority among OD/DRS projects. The Division's management analysis staff has been strengthened with measurable results. The availability of meaningful workload data has proven to be of invaluable assistance to the Financial Management Branch, OAM, by significantly reducing the amount of time required to convert operations to fee-for-service financing. Prior to implementation of the current work measurement system, financial accounting studies required 8 to 12 months to accumulate cost data. Cost feasibility can now be determined within a matter of weeks. An important feature of the management reporting system is the identification, by I/D's of how DRS manpower resources are distributed. The impact of I/D program changes can be evaluated more precisely knowing the approximate percentage of manpower provided to a specific Institute.

Training

The Division continues its efforts to develop and implement a career development training program for personnel at all grade levels. Additional needs will be identified during FY 1969, with priority given to improved management development of Branch Chief and key line personnel. Training and management goals will be explored and defined with the objective of developing an environment which will increase cross-pollenization of ideas at every working level.

Supervisor-employee relationships will be examined and strengthened with major emphasis placed on techniques for developing employee commitment to the overall mission of the Division. A full-time Training Officer will be assigned to the Division to serve as a stimulant, resource, and focal point for all training and development activities.

Construction

In FY 1968, a record pace continued in design and construction associated with the expansion of NIH facilities. The current program includes more than 20 projects in various stages of planning, design, or construction, having a total cost in excess of $100 million. Eleven projects were under construction during the year. The Gerontology Research Center, a 200,000+ square foot laboratory building located on the Baltimore City Hospitals grounds, was completed. Also, three major construction projects were carried to virtual completion during the year. The projects are the NCI Virus Isolation Facility, located southwest of the National Library of Medicine, the Library and Cafeteria additions to the south side of the Clinical Center, and the 2-story addition to Wing D, south side of the Clinical Center. On the NIH reservation, major expansion of the utilities distribution system disrupted many roads and parking areas with some personal inconveniences. The major part of this work is now finished. The design of several projects, including two multilevel parking facilities, is nearly complete and these projects should be under construction next year.

Animal Programs

Major emphasis was placed upon data processing of production and animal issue information, to achieve greater efficiency in the utilization of limited production facilities. Efforts were also made to establish more meaningful communications with the Institutes and Divisions regarding their current and future requirements for experimental animals.

Programs to improve the quality of all animals furnished to intramural research programs were continued and intensified. For the first year in recent history, the rodent and rabbit production colonies experienced no major outbreaks of disease. Significant improvements were made in the quality of the random source dogs and cats issued. This is directly attributable to the lengthening of the conditioning period from 30 to 45 days.

A development of singular importance, the successful establishment of a large colony of donor dogs to furnish whole blood, has resulted in a significant reduction in the numbers of dogs required for research purposes at NIH. The furnishing of blood, coupled with improvements in the health status of conditioned random source dogs, reduced the needs for dogs by 786 animals. Projected dog issues for the year will be 3,612, the fewest number of dogs issued since FY 1960.

Library Services

The NIH Library moved into a new facility, providing more than twice as much total space, 42,500 square feet, and accommodating twice as many patrons as the former Library.

A journal evaluation was conducted by 75 scientists representing various subject specialties. A listing of periodical titles recommended for addition to the collection has been compiled. A list of titles recommended for deletion is in process.

Automation within the Library Branch was concentrated in two areas: businesslike transactions, such as serials recording and acquisitions, and publications. Automation of circulation procedures, including overdues, was also given some attention.

A total of 39,000 books and journals were circulated during FY 1968. Approximately 7,500 were loaned, and 8,500 were borrowed from other libraries. Approximately 5,200 copies of translations were provided to other libraries. Also, the Library's collection was strengthened by the addition of 4,500 new books and by the receipt of 500 books through gift and exchange. For FY 1968, the Library placed subscriptions to more than 2,227 journal titles and received an additional 800 as gifts or on exchange.

The Branch Chief announced his resignation effective July 15, 1968, to accept appointments as Director, Health Sciences Library, and Associate Professor of Medical Librarianship at Temple University.

Biomedical Engineering

Major emphasis is placed on direct collaboration between BEIB professional staff and intramural researchers in the conduct of biomedical research and development programs. In addition, individual improvement is promoted through an education and training program to further enhance the Branch's capabilities and effectiveness. BEIB has now gained a reputation as a national focal point for engineering competence and authority in biomedicine.

The Instrument Fabrication and Systems Maintenance Sections achieved unprecedented peaks in productivity during FY 1968. These sections performed 11,550 assignments during the year at a value of $1,026,000--an increase of 5 percent in jobs and 11.3 percent in dollars over the previous annual high, reached in FY 1967.

Branch professional staff have been involved in approximately 400 research and development tasks. The year has seen especially noteworthy original contributions in the areas of artificial organs, materials, laser technology, mechanization, automation, physiological monitoring, patient care, and physiological systems analysis.

A modest program has been initiated for more economic use of scientific equipment. Experience to date shows growing acceptance of the concept by the NIH community.

D. Problems

Construction

Progress of the facilities design and construction program continues to be hindered by a number of problems. Specific programs (NIH Animal Center, Phases IA and II, Building 31 Multilevel Parking, etc.) have not progressed on schedule. In some cases, time extensions of the design phase have seriously delayed the start of the construction of the project and the eventual beneficial occupancy of the facility by the client program. In other instances, programs have been delayed as early as the POR stage or prior to the design phase. Typically, the reasons for these time delays in the design program may be classified as (1) funding problems, and (2) reviewing by groups outside NIH.

The time required for obtaining approvals from numerous outside groups, such as PBS, Bureau of the Budget, Fine Arts Commission, NCPC, and the Maryland-National Capital Park and Planning Commission, has slowed the progress of NIH construction programs. Another problem is that these groups are physically located at a distance from NIH and have no immediate commitment to NIH programs and little reason, from their viewpoint, to hasten the progress of construction projects. However, the new reorganization within the Department, including decentralization of some approvals, may help to improve this situation since some decisions can now be made at the NIH level. The reorganization may also lead to development of an improved, more direct system of construction control.

Delays during the construction period are usually due to delays in submission, approval, procurement, and delivery of specialized items of equipment, and failure by the contractor to properly schedule and coordinate his work. Overriding defense priorities have delayed manufacture and delivery of some items of equipment, particularly electrical items.

The lack of sufficient personnel and increased workload in the Design Division of PBS have seriously extended contemplated review periods and suspended progress. Decentralization of design authority to the GSA Regional Offices may improve the design schedules. The assignment of aggressive project coordinators at the PBS has improved this situation considerably.

Program Planning

The difficulty of coordinating service needs with I/D demands continues to be a major operating problem in this Division. The critical timing in the fiscal cycle precludes us from preparing a budget based on the estimated needs of the Institutes. This problem is complicated by legislative changes in I/D budgets which occur too late to incorporate in a service organization's plans. During FY 1968 the Director of DRS met with the Scientific Directorate of a major Institute to explore means of solving this problem. The response was enthusiastic and similar meetings will be held at 6-month intervals in the future. While the eventual success of these efforts cannot be precisely determined, it is planned to expand this concept to other I/D's during FY 1969.

Staffing for Key Positions

The recruitment difficulties prevalent throughout NIH continue to plague the Division of Research Services. This problem is intensified in an organization like DRS, where research understandably has lower priority than services. The Division continues to work with the Personnel Management Branch to raise the image of professional personnel in service organizations and improve the competitive position of the Division of Research Services for engineers, veterinarians, photographers, librarians, etc.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1967, through June 30, 1968

RESEARCH FACILITIES PLANNING BRANCH

Howard M. Biggs
Branch Chief

I. SUMMARY

Design and construction associated with the expansion of NIH facilities continued at a record pace in FY 1968. The current RFPB program includes more than 20 projects in various stages of planning, design, or construction, having a total cost in excess of $100 million. Seven projects were under construction during the year, and one was completed--the Gerontology Research Center, a 200,000+ square foot laboratory building, located on the Baltimore City Hospitals grounds. On the NIH reservation in Bethesda, major expansion of the utilities distribution system disrupted many roads and parking areas with some personal inconveniences. The major part of this work is now finished. The design of several projects, including two multilevel parking facilities, is nearly complete and these projects should be under construction next year. Budgetary restriction severely reduced our Development Section program; however, a limited number of design guidelines and material studies were completed for use by both NIH and other medical research institutions.

Favorable working relations with representatives of the Public Buildings Service (PBS) of the General Services Administration (GSA) in both the Central and Regional Offices continue to be essential to the success of the NIH construction program. Constant effort is being made to improve and strengthen these relationships. At the present time GSA is utilizing Architect/Engineer personnel for the detailed inspection of construction on the majority of NIH projects. These engineers work directly under the supervision of the PBS Region 3 Project Manager, and the arrangement has proven to be reasonably satisfactory to date.

GSA has recently adopted a design decentralization policy which places major design supervision responsibility on its regional offices. Authority for supervision of design of NIH projects has thus been delegated to Region 2 in New York (for Puerto Rican projects), Region 3 in Washington, D. C. (for D. C., Maryland, and Virginia projects), and Region 4 (for North Carolina projects). Region 3 has a limited professional staff which will require augmentation to effect an adequate program of design supervision. Our experience with this new delegation of authority is too limited for any further appraisal at this time.

The reviews and appraisals of proposed NIH facilities by other agencies such as GSA, the National Capital Planning Commission (NCPC), The Commission of Fine Arts (CFA), and the Maryland-National Capital Park and Planning Commission (MNCPPC) continue to extend the time for approval of projects. Design schedules for some facilities (Warehouse, NIMH Child Research Center, etc.) have been extended through the implementation of studies associated with estimated budget deficits, master site planning, reservation parking, and other specific problems.

Communications between NIH personnel and those of the NCPC, the MNCCPC, the Washington Metropolitan Area Transit Authority (WMATA), and the Washington Suburban Transit Authority (WSTA) have improved steadily. RFPB has been able, through diligent effort, to establish a good rapport with these agencies. Negotiations for additional sanitary sewer capacity were amicably completed with the Washington Suburban Sanitary Commission (WSSC) in October 1967.

II. BRANCH PROGRAMS

A. Objectives

The major objective of RFPB is coordinating the planning and construction of new facilities on the NIH reservation and at its field stations. A secondary objective is providing development engineering services and technical assistance where special problems in design or construction are encountered.

B. Current Programs

The Design Section is primarily responsible for assuring that new construction provides for the program needs of NIH research scientists. A staff of professional engineers renders limited consulting service and provides coordination between contract architects, PBS (GSA), NIH research staff members for whom facilities are being provided, and other concerned branches of the Division of Research Services.

The Construction Section provides close technical control over new facilities for NIH during the construction phase. A staff of management engineers maintains surveillance during construction to determine that the facility is built according to plans and specifications, with particular emphasis on those aspects peculiar to NIH requirements.

The Development Section program is one of technical assistance and is directed toward improving the functional aspects of facilities presently under design, as well as contributing standards, recommendations, and solutions to operational problems encountered in existing NIH facilities.

Members of the RFPB staff are frequently called upon to confer with visiting research scientists and engineers on current concepts, techniques, and practices in the design and construction of biomedical research facilities. These visitors represent a broad spectrum of national and international medical research activities, both government and private.

C. Progress and Accomplishments (for a summary of all design and construction projects, see attached Tables I and II, respectively)

Multilevel Parking Facility for NCI-NIMH/NINDB Buildings

Planning funds for this project to provide a multilevel parking structure for 825 cars were appropriated in FY 1966. The POR for this facility was forwarded in March 1966, through channels, to the BOB. In September 1966, the BOB approved the POR after requesting that NIH make a comprehensive study of various aspects of parking, including methods of operating a multilevel parking garage. This study was completed and a report forwarded, through channels, to the BOB in April 1967. In November 1966, GSA negotiated a design contract with the A/E firm which had designed the NCI-NIMH/NINDB Building complex. Conceptual pre-diagrammatic sketches were submitted to GSA in March 1967. The diagrammatic sketches were approved on July 11, 1967. The tentative sketches were approved on November 13, 1967, and the intermediate working drawings were approved on April 8, 1968. Complete working drawings are scheduled for submission on June 3, 1968, and final working drawings on July 10, 1968.

It is estimated that the project will be advertised for construction bids in August 1968 and that construction will start in October 1968.

NIH Animal Center, Phase IA

This project includes a general laboratory building, animal behavior laboratory, and waterfowl habitat for the NIMH; and a primate building for Laboratory Aids Branch, DRS. After approval of revised tentative sketches in August 1965, this project was delayed by the A/E's requests, first, for an additional fee and later, for the termination of his contract. Each of these requests was denied by GSA. Upon official notification in December 1965 to proceed with design, the A/E resumed work. Intermediate working drawings were received by GSA in April 1966. However, the GSA cost estimate, based on the intermediate working drawing submission, exceeded available funds by $178,000. NIH, GSA, and the A/E decided that construction costs could be substantially reduced by relocating the Primate Building. Since this requirement constituted a change in scope of the A/E's contract, the A/E requested an additional fee. At this time the design program was further delayed while the NIH request for $25,000 additional planning funds was approved by the BOB and the funds transferred to GSA. The A/E resumed work in October 1967 and submitted complete working drawings in late January 1968. The design of this project should be completed in late FY 1968. PHS deferred construction of this project until FY 1969.

NIH Animal Center, Phase II

This project includes an agricultural management building, animal production facility, a third residence, incinerator, and necessary supporting utilities and grounds improvements. The POR was approved by NIH and forwarded, through channels, to the BOB in November 1965. The BOB delayed approval of the POR and deferred action on a request for apportionment of the planning funds pending receipt and evaluation of additional justification for the project. Late in April 1967, the BOB gave informal approval to proceed with this project. The POR was revised in accordance with BOB approval and forwarded to GSA in December 1967. A design contract was negotiated by GSA, Region 3, in March 1968 with Lucius R. White, Jr. and Edward C. White in a joint-venture with Sanders & Thomas. Design should be completed in the fourth quarter of FY 1969, and construction should start in the first quarter of FY 1970.

Multilevel Parking Facility for Building 31

This $1,600,000 project is for a 650-car parking garage to serve the occupants of the new wing on Building 31. The building is being designed by a joint-venture of Keyes, Lethbridge & Condon and Cochran, Stephenson & Donkervoet, the same firm which designed Building 31. The diagrammatic sketches were submitted by the A/E in June 1967. The project was approved by The Commission of Fine Arts in June 1967 and by the National Capital Planning Commission in July 1967. The NIH review comments on this submission were transmitted to GSA in August 1967 and the diagrammatic sketches formally approved by GSA in September. The A/E completed the tentative sketches and submitted them in November 1967. The NIH comments were forwarded to GSA in December 1967; however, the GSA review indicated a $795,000 deficit in the project cost. Preliminary soil boring tests which were completed in January 1968 also indicated that, because of underground water, extensive redesign might be necessary. GSA suggested a major reduction in the size of the building to offset these two problems (the budget deficit and the costly foundation design). In February 1968, RFPB strongly recommended that PBS explore in greater detail these two problems before directing the A/E to take such drastic action. The extent of the groundwater problem was greatly reduced at a meeting in April 1968 and in subsequent correspondence, but a major funding deficit still remains.

Currently, the A/E is revising his construction cost estimate and preparing engineering recommendations. RFPB feels that some reduction in the size of the garage may be required. The future design and construction schedule is indeterminate pending the resolution of the major funding deficit.

NINDB/NICHD Research Facility, Puerto Rico

The selected A/E for this design project is Isadore & Zachary Rosenfield, Fred S. Dubin & Associates, and Efrain E. Perez-Chanis, who received the notice to proceed with the design in May 1966. The diagrammatic sketches were submitted in August 1966. They were not approved at that time due to an estimated budget deficit of $187,000. Revised diagrammatic sketches were resubmitted in December 1966 and were approved by GSA in January 1967.

At the completion of FY 1967, the project's estimated construction cost was over its $1,972,000 budget by $300,000 due to a projected 14 percent per year cost escalation in San Juan, Puerto Rico. On July 12, 1967, the Director, DRS, ordered the size of the building reduced to bring the project's cost within the existing budget. After careful reviews and consultations with the two client institutes, RFPB forwarded a list of research space reductions to PBS in August 1967. At a subsequent GSA-NIH-A/E meeting in September 1967, it was agreed to reduce the size of the planned building rather than start a complete redesign. (In early January responsibility for design supervision of the project was transferred from the Central Office of GSA to Region 2 of GSA.) The revised tentative sketches were submitted by the A/E in February 1968 and approved by NIH in March 1968. GSA formally approved the revised tentative sketches in April 1968. Currently, the A/E is preparing the intermediate working drawings which are scheduled for completion in June 1968. The complete working drawings are scheduled for completion by October 1968. Construction should start in January 1969, and beneficial occupancy should occur in the late summer of 1970.

NINDB-NICHD Experimental Facility, Sabana Seca, Puerto Rico

This project is an experimental animal compound to be built on land declared surplus by the U. S. Navy in Sabana Seca, Puerto Rico. The final POR was forwarded from RFPB to DRS on July 11, 1967. After reviewing the project, the Bureau of the Budget apportioned the requested $200,000 for funding in September 1967. The Caribbean Division, Naval Facilities Engineering Command in San Juan, Puerto Rico, agreed to design the project on an "in-house" basis. In January 1968, an agreement for design and construction services was formally accepted by the Caribbean Division, Naval Facilities Engineering Command. Design has moved very rapidly since then. The 30 percent drawings were received in March 1968; the NIH review and approval were also completed in March 1968. The final drawings will be reviewed by NIH in June 1968. A construction contract for the project should be awarded in July 1968 and the construction completed in December 1968.

Combined Service Facility and Warehouse

Notice to proceed with the design of the Phase I Warehouse was given to the selected A/E firm by GSA in May 1965. In the diagrammatic submission of June 1965, the A/E's construction cost estimate was $120,000 higher than the $670,000 sum available for the award of a construction contract. However, GSA estimated at this stage that the facility could be constructed within available funds. Because GSA failed to give the A/E a notice to proceed with the development of a master plan for the warehouse area until October 1965, tentative sketches were not received until December 1965. The A/E's cost estimate at the tentative stage was $1,099,536, approximately $430,000 above the funds available for the construction contract award. Numerous studies were made by RFPB, GSA, and the A/E in an effort to reduce the cost of the project. All work on the project was deferred in January 1966, pending completion of the Master Site Plan for the southern portion of the NIH reservation, the Materials Handling Study, and the Incinerator Study. A new POR has now been prepared for the Phase I Warehouse and the Combined Service Facility to be accomplished as a single project. Approval by NIH of this POR is anticipated in July 1968.

Child Research Center (NIMH)

The original design for this facility was stopped at the completion of tentative sketches. In November 1965, progress beyond this stage was delayed pending a resolution to the community-sponsored recommendations for the extension of Woodmont Avenue through a portion of the NIH reservation to Wisconsin Avenue. This extension necessitated a new site for the CRC facility. Accordingly, in July 1966, NIH requested GSA to proceed with the design of the Center on a site in the southwest corner of the NIH reservation. Negotiations between the A/E firm, Johannes & Murray & Associates, and GSA delayed the initiation of the new design contract until December 1966. A revised site plan was submitted by the A/E in January 1967. Significant delays were incurred in obtaining the National Capital Planning Commission's approval of the site layout plan. The plan was finally accepted and the design should be completed in November 1968. In April 1967, at the request of GSA, DHEW reluctantly agreed to budget for construction funds for the project which originally were in a GSA appropriation. The funds were not provided in the FY 1969 DHEW program, but may be requested in the supplemental FY 1969 program. A year's delay could result if the funds are not provided in the FY 1969 budget.

NICHD Research Facility

The design of this $9,650,000 research facility began early in FY 1968. The architectural firm of The Architects Collaborative, Cambridge, Mass., was recommended by DHEW in the spring of 1967 and the formal negotiations were successfully concluded in August 1967. The A/E was given the notice to proceed in September 1967. The firm submitted their diagrammatic sketches in January 1968. The NIH approval of the drawings occurred in February 1968; the formal GSA approval in March 1968. The project has been approved by NCPC and FAC. The tentative drawing submission is scheduled for June 1968. The design should be completed in April 1969; the beneficial occupancy is planned for August 1971.

Master Utilities Extension

This program is divided into two major phases: Phase I, which includes extension and expansion of utility systems required to supply those new facilities under construction, or recently completed; and Phase II, which will provide utilities for the remainder of the proposed buildings. The estimated cost for Phase I planning and construction is $9,850,000. One part of the Phase I work was accelerated in order to meet the immediate needs of Buildings 12A and 29A. This work, Phase IA, was completed in January 1966. Other portions of the Phase I program have also been accelerated in order to provide additional steam and refrigeration capacity required for the construction program. The Ninth Refrigeration Increment installed in Building 11C was completed this year. Construction on the new chilled water plant, Building 34, which will furnish chilled water for Buildings 35, 36, 37, as well as others, was started in January 1967 and is proceeding on schedule. A construction contract for the 4th boiler and the conversion of the chilled water system to year-round operation was awarded to The W. G. Cornell Company in September of 1967 and should be complete by December 1968. Construction of a new NIH/PEPCO joint-use substation was begun by PEPCO in May 1968. A contract for the NIH equipment was awarded in June 1968, and work should be completed by August 1969. This will complete all Phase I construction.

Current estimates for Phase II work indicate a total estimated cost of approximately $5,788,000. This project will provide utility services to all new buildings including the Fogarty Center, OAM Combined Service Facility, the NICHD Building, NLM Extension, the Child Research Center, etc. The POR for this project should be ready for submission, through channels, early in FY 1969.

National Environmental Health Sciences Center (NEHSC)

Planning funds for this project were appropriated in FY 1961 and FY 1965. In August 1966, responsibility for the planning, design and construction of the NEHSC was transferred to NIH. These facilities, as well as the National Center for Air Pollution Control, will be constructed on a portion of the 509-acre site located at Research Triangle Park, North Carolina. The POR for the Master Site Plan of the 509-acre site was prepared by the Division of Buildings and Facilities, OSG, PHS. In May 1967, PHS forwarded this POR, through channels, to the BOB for approval. BOB approved the Master Site Plan POR in February 1968. The award of an A/E contract for the Master Site Plan is anticipated in June 1968, and the Master Plan should be completed by July 1969. A POR for permanent facilities for NEHSC should be completed concurrently with the Master Plan. Construction of NEHSC is scheduled to start in the first quarter of FY 1972.

John E. Fogarty International Center for Advanced Study in the Health Sciences

$500,000 was appropriated in FY 1968 for planning the Fogarty Center. The POR was begun in October 1967 and submitted in April 1968 to the Director, NIH, for approval and transmittal to the BOB for apportionment of the planning funds. $6,475,000 is being requested in the FY 1970 budget for the construction of the project including the extension of the master utilities and multilevel parking.

Additional Multilevel Parking Facility for Building 31

Planning funds for this project are included in the FY 1968 budget. A first draft of the POR was prepared early in 1968. The final draft of the POR was completed and distributed in May 1968. It is anticipated that a design contract for the project could be awarded by October 1968.

Master Site Plan for Southern Portion of the NIH Reservation and Tunnel Feasibility Study

This study, initiated in late FY 1966 on the recommendations of the NCPC, provides more intensive planning for development of the southern portion of the NIH reservation. Specific problems associated with the site selection for the Warehouse Facility and warehouse operation were investigated by the consultant A/E firm of Smith Haines Lundberg and Waehler. In July 1967 the plan was approved by the National Capital Planning Commission. The final report and study were submitted by the consultant in February 1968.

General Office Building Extension, Building 31C

This project was authorized in FY 1962 with an appropriation of $700,000 in planning funds. The complete working drawings were submitted in August 1965 and approved by GSA in October 1965. At this point, it was decided to incorporate a portion of the required utilities construction with this project in order to insure timely completion for occupancy and to avoid conflicts during construction. Final working drawings of the building and related utilities were completed in December 1965 and March 1966, respectively. The project was advertised in May 1966, and construction bids were opened in July 1966. However, because of ambiguities in the construction documents, as interpreted by the GAO, GSA rejected all bids for the project. Accordingly, the project was readvertised, and in December 1966 the Norair Engineering Corporation was awarded a construction contract totaling $5,844,000. Construction started in January 1967 under unfavorable weather conditions which slowed up initial work. Subsequent progress has, in general, been satisfactory; however, there have been some intermediate delays. Construction was 70 percent complete at the end of FY 1968, and the estimated completion date is now December 31, 1968.

NCI-NIMH/NINDB Cafeteria, Buildings 35, 36, and 37

The construction contract for this building complex was awarded August 27, 1965, to the Blake Construction Company at a cost of $16,782,000, which includes the contractor's base bid of $14,728,000 and alternates valued at $2,054,000. The complex includes a six-story structure and basement for the NCI, a five-story structure and basement for NIMH/NINDB, and a one-story Cafeteria with basement. The construction contract allows 26 months for completion. Initial construction progress was excellent. However, a serious dispute over the poor quality of work on the Cafeteria roof delayed construction on this building approximately one year, and disputes over special equipment items have delayed completion of the laboratory building. Construction work on the project was essentially completed in FY 1967, but beneficial occupancy will be delayed several months.

Gerontology Research Center, Baltimore, Maryland

Located on the grounds of the Baltimore City Hospitals, adjacent to the main hospital building, this four-story structure with a two-story mechanical wing is being constructed by John McShain, Incorporated, at a contract cost of $6,989,000. The construction contract was awarded on October 31, 1965. Hindered by inclement weather during its initial construction stages and delays in approval and delivery of casework and environmental chambers, final completion was delayed about eight months. Gerontology Research Center personnel began occupancy of the building in February 1968.

Development Projects

Program studies, the majority of which are of short duration, are reported and distributed internally to interested NIH organizations and/or published in trade journals. Requests from extramural activities for available information are also filled. Limited research contracts continue to be an effective means for improving the quality of work and conserving manpower and money. Such contracts also increase program flexibility and provide detailed specialization where required.

Collaborative Projects

Improving animal care facilities (in collaboration with the Laboratory Aids Branch).

The vital importance of laboratory animals to health research has accentuated the need for better quality animals. In recognition of this need, a research and development program to improve animal care and facilities has been in progress for several years. The studies include: (a) the development of caging systems, particularly for the NIH Animal Center, Phase IA and Phase II; and (b) the development of the automated equipment and care procedures with emphasis on watering, feeding, and cage cleaning techniques.

RFPB also provides technical assistance and advice to other NIH groups in preparing design guidelines, criteria, specifications, and standards for equipment and facilities.

As a means of stimulating new approaches and introducing new concepts, several visits to other laboratory and animal facilities were made. Information from private institutions, as well as other government facilities, has served to foster novel ideas and solutions to operational, design, and construction problems here at the NIH.

Informational Reports

1. A Study of One-Way Mirrors
2. Cost Data for Partition Walls
3. Laboratory Furniture and Equipment, Installation and Construction
4. Waste Piping Materials
5. Economic Analysis of Fume Hood Operation

D. Problems

Progress of the facilities design and construction program continues to be hindered by a number of problems. Specific programs (NIH Animal Center, Phases IA and II, Building 31 Multilevel Parking, etc.) have not progressed on schedule as planned. In some cases, time extensions of the design phase have seriously delayed the start of the construction of the project and the eventual beneficial occupancy of the facility by the client program. In other instances, programs have been delayed as early as the POR stage or prior to the design phase. Typically, the reasons for these time delays in the design program may be classified as (1) unrealistic time schedules,

(2) funding, and (3) reviewing by groups outside PHS. Delays during the construction period are usually due to delays in submission, approval, procurement and delivery of specialized items of equipment, and failure by the contractor to properly schedule and coordinate his work. Overriding defense priorities have delayed manufacture and delivery of some items of equipment, particularly electrical items (switchgear, controls, etc.).

Remedial action has been taken wherever possible. RFPB has encouraged the establishment of more realistic review periods in design contracts. The lack of sufficient personnel and increased workload in the Design Division of PBS have seriously extended contemplated review periods and suspended progress. Decentralization of design authority to the GSA Regional Offices may improve the design schedules; however, some additional orientation problems are anticipated. Representatives of both DRS and RFPB have brought these scheduling problems to the attention of responsible GSA officials in frequent attempts to expedite design progress. The assignment of aggressive project coordinators at the PBS has improved this situation considerably.

Some examples of major design delays in specific program areas are as follows:

1. Insufficient funds to adequately design Phase IA of the NIH Animal Center has delayed this project from April 1966 to FY 1969.

2. The design program of the NIMH Child Research Center has experienced extensive delays due to the pressure of community groups (MNCPPC and NCPC) in connection with the proposed siting.

3. The Phase II design program of the NIH Animal Center was delayed at the POR stage for more than 18 months pending the review of the initial POR by the BOB. An additional six months was required to revise the POR in accordance with the BOB budgetary restrictions.

4. The Warehouse Extension project has been deferred for more than two years pending the completion of studies for NIH related to siting and materials handling.

5. Delays in Phase II, MUE project due to deferment of funding by BOB.

6. Resolution of differences in the GSA and A/E cost estimates has delayed design progress on the Building 31 MLP facility for more than six months.

Some examples of major delays in the construction program are as follows:

1. Contractor's refusal to accept GSA direction to remove and replace the Cafeteria roof delayed work on this building over 12 months.

2. Resolution of discrepancies in painting of casework delayed installation and completion of this work several months on both the NCI-NIMH/NINDB Buildings and the Gerontology Research Center.

3. Contractor's failure to promptly schedule, submit, and order electrical switchgear delayed completion of the new Chiller Plant two months.

4. On the NCI-NIMH/NINDB Buildings the contractor's refusal to comply with contract requirements for prequalification of manufacturers of the environmental chambers and cage washing equipment required GSA to procure these items on a separate basis. This will result in an estimated delay of nine months in supplying these services and facilities to the buildings.

RFPB is continuing to pursue these problems to alleviate the causes.

PBS, which has direct responsibility for construction contract administration, continues to encounter difficulty in hiring and retaining competent personnel for construction supervision and inspection. Current A/E contracts for design of NIH facilities include an optional provision for supervision of the construction by the A/E, under the direction of the PBS Project Manager, when PBS personnel are not available.

E. Program Plans

Pending reorganization plans for engineering resources in DRS will have some effect on RFPB program plans. In any case, the ongoing construction program will continue to require careful planning, coordination, and cooperation to avoid interruption and interference with NIH research activities. In addition, major effort is required to resolve the continuing problem of program delays and assure timely completion of facilities.

The development program will continue to place strong emphasis on the design-support function for the NIH facilities planning, design, and construction program. Areas of investigation presently being studied in depth are as follows:

1. Specification for Cold and Constant Temperature Rooms
2. Specification for Cage and Rack Washers (ESB)*
3. Specification for Conveyor-Type Cage Washers (ESB)*
4. Laboratory Sealants
5. Water Still Specification
6. Use of Disposables (Glassware, etc.)
7. Ventilation Standards (ESB)*
8. Electromagnetic Shielding
9. Air Balancing
10. Cathodic Protection

*Denotes collaborating organization.

TABLE I - RFPB - FY 1968 Program of Authorized Design Projects

Project	Design Completion Date	Construction Completion Date	Construction Cost*	Planning Cost	Total Project Cost	A/E Designer
NCI-NIMH/NINDB Multilevel Parking Facility	7/68	11/69	$ 1,985,000	$ 125,000	$2,110,000	SH & GA, Inc.**
NIH Animal Center Phase IA	6/68	2/70	1,325,000	125,000	1,450,000	Heery & Heery
NIH Animal Center Phase II	6/69	6/71	4,822,000	440,000	5,262,000	White & White with Sanders & Thomas
Multilevel Parking Facility, Bldg. 31	1/69	4/70	1,505,000	95,000	1,600,000	K, L, & C and C, G, & Van A**
NINDB-NICHD Research Facility, P.R.	10/68	7/70	2,172,000	148,000	2,320,000	R, D, and C**
Sabana Seca Facility Puerto Rico	6/68	12/68	188,140	11,860	200,000	Navy, San Juan,P.R.
Combined Service Facility & Warehouse	9/69	4/71	3,523,500	256,500	3,780,000	Not selected
Child Research Center (NIMH)	11/68	5/71	1,285,000	156,000	1,441,000	J & M**
NICHD Research Facility	4/69	8/71	9,640,000	850,000	10,490,000	The Architects Collaborative

Project	Design Completion Date	Construction Completion Date	Construction Cost*	Planning Cost	Total Project Cost	A/E Designer
Master Util. Phase I	9/67	12/68	$ 9,341,600	$ 522,000	$ 9,856,600	HDNA**
National Environmental Health Sciences Center, North Carolina	5/71	9/74	37,860,000	3,420,000	41,280,000	Not selected
John E. Fogarty Center	1/70	12/71	5,880,000	500,000	7,000,000	Not selected
Additional Multi-level Parking for Building 31	6/69	7/70	1,410,000	100,000	1,510,000	Not selected
Master Site Plan for Southern Portion of the NIH Reservation & Tunnel Feasibility Study	2/68	N.A.	N.A.	21,000	N.A.	SHLW**

Footnotes:

* Includes construction contract, contingencies, and other construction costs.

** SH & GA, Inc. - Smith, Hinchman & Grylls Associates, Inc.
K, L, & C - Keyes Lethbridge & Condon - C, G, & Van A. - Carroll, Grisdale, & Van Alen
R, D, & C - Isadore and Zachary Rosenfield, Fred S. Dubin Associates, and Efrain E. Perez-Chanis
J & M - Johannes & Murray & Associates
HDNA - H. D. Nottingham & Associates
SHLW - Smith Haines Lundberg & Waehler

N.A. - Not applicable

TABLE II
NEW CONSTRUCTION - FY 1968

Project	Design Completion (Date)	Contract Award (Date)	Construction Schedule (Months)	Estimated Completion (Date)	Contract Overrun (Months)	Contract Amount *	Contractor
NCI-NIMH/NINDB Cafeteria A/ Buildings 35, 36, and 37	4/65	9/18/65	26	5/31/68	8	$16,782,000	Blake Constr. Co., Inc.
Gerontology Building B/ Baltimore, Maryland	5/65	10/31/65	23	2/5/68	5	$ 6,989,000	John McShain, Inc.
MUE-IB, Bldg. 34 & C/ Misc. Outside Services	9/66	1/13/67	20	9/13/68	-	$ 4,643,900	Norair Engr. Corp.
MUE-IB, Bldg. 11-C, 9th C/ Refrigeration Increment	5/66	8/15/66	11	7/15/67	1	$ 740,000	John C. Grimberg Co.
General Office Building D/ Extension, Building 31C	1/66	12/22/66	22	1/2/69	-	$ 5,844,000	Norair Engr. Corp.
MUE-IB, 4th Boiler & C/ Year-Round Air Conditioning	4/67	8/3/67	16	12/1/68	-	$ 765,000	W. G. Cornell Co. of Wash., Inc.
MUE-IB Substation Equip. C/ and Utilities	12/67	6/15/68 1/	13	7/20/69 1/	-	$ 359,150 2/	

Architect/Engineers

A/ Smith, Hinchman & Grylls Associates, Inc.
B/ Cochran, Stephenson & Donkervoet and Lucius White, Clay & White
C/ H. D. Nottingham & Associates
D/ Keyes, Lethbridge & Condon and Carroll, Grisdale & Van Alen
1/ Approximate dates - No contract award has been made
2/ Low bid with all alternates
* Does not include contingencies, supervision, or planning

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1967, through June 30, 1968

PLANT ENGINEERING BRANCH R. R. Holliday, Chief

I. SUMMARY

During FY 1968, the Plant Engineering Branch met all service demands with a personnel increase of only 7 percent, or 35 positions (as of May 1, 1968). Twenty-eight of these were added to the staff of the Maintenance Engineering Section to operate and maintain the utility systems of new buildings, with the remaining seven assigned to other supporting functions.

Three major construction projects were carried to virtual completion during FY 1968. The projects are the NCI Virus Isolation Building, located southwest of the NLM, the Library and Cafeteria additions to the south side of the Clinical Center, and the two-story addition to Wing D, south side of the Clinical Center. The total cost of these projects approximates $6 million.

Efficiency of boiler operation in the central power plant was increased by about 4 percent. Studies of other utility systems were inaugurated in an effort to improve operations and reduce costs.

II. BRANCH PROGRAMS

A. Objectives

The mission of the Plant Engineering Branch is to provide responsive support to the medical research mission of the National Institutes of Health by fulfilling, as expeditiously and as economically as possible, the functions described below.

B. Current Programs

Operation and Maintenance: Consists of operating and maintaining the NIH physical, mechanical, electrical, architectural, and landscaping facilities.

Engineering: Consists of developing and preparing plans and specifications for repairs, alterations, and improvements to NIH facilities; administering and inspecting work performed by private contractors; and providing engineering services as required.

Construction: Consists of providing craft services (station labor) for altering, repairing, and improving NIH facilities.

C. Program Progress and Accomplishments

Work Performed By Station Labor: Requests for PEB services are received in the form of written work requests and by telephone. Telephone requests for minor services such as clogged plumbing, light bulb replacement, air conditioning malfunctions, and utility leaks are received by three decentralized area maintenance units. All written requests are received by one central work reception office.

An average of 1500 telephone requests are received each week, while written orders average about 360 per week. Almost all telephone requests and about 60 percent of the written orders require little or no formal planning (plans, special material, or detailed estimates of labor). About one percent of the written orders, however, require the services of professional engineers for planning, and most of these projects are performed by private contractors rather than by station shops. No additional personnel were employed during the year for station shop activities. An examination of material expenditures for these activities indicates that gross work output remains high.

Chart I reports material expenditure trends by quarter since 1963. The dollar value of material expenditures during the year appears to be starting an upward trend over the previous year.

A good measure of the adequacy or responsiveness of the station shops service is the work in backlog. Experience has shown that an eight-week backlog will allow the most responsive service without sacrificing efficiency. Charts II and III report the backlog trend for the central craft shops since August 1965. The backlog during FY 1968 has remained level at about ten weeks, indicating that responsive service was provided.

Construction By Private Contractors: Most large jobs, estimated to require 350 or more manhours, are constructed by private contractors. Work awarded since FY 1964 has been as follows:

Fiscal Year	No. of Contracts	Dollar Value
1964	218	3,016,000 1/
1965	178	2,250,000
1966	152	7,735,000 2/
1967	132	2,500,000
1968	169	4,500,000 3/

1/ Included Building 12A ($1,440,661)
2/ Included the NCI Virus Isolation Facility ($3,188,000) and the Library and Cafeteria and Wing D Additions to Building 10 ($2,752,000)
3/ These figures include work awarded through March and estimates of work scheduled to be awarded prior to July 1, 1968.

Construction for Direct Research Support

NIH Library Relocation

In 1964, $900,000 was appropriated for the planning and construction of new library facilities for the National Institutes of Health. The POR was completed in December of 1963 and design was completed in November 1965. The construction contract was awarded in April 1966 and is complete except for minor items,

NATIONAL INSTITUTES OF HEALTH
Division of Research Services - Plant Engineering Branch

MATERIAL SUMMARY

Quarters (fiscal year)

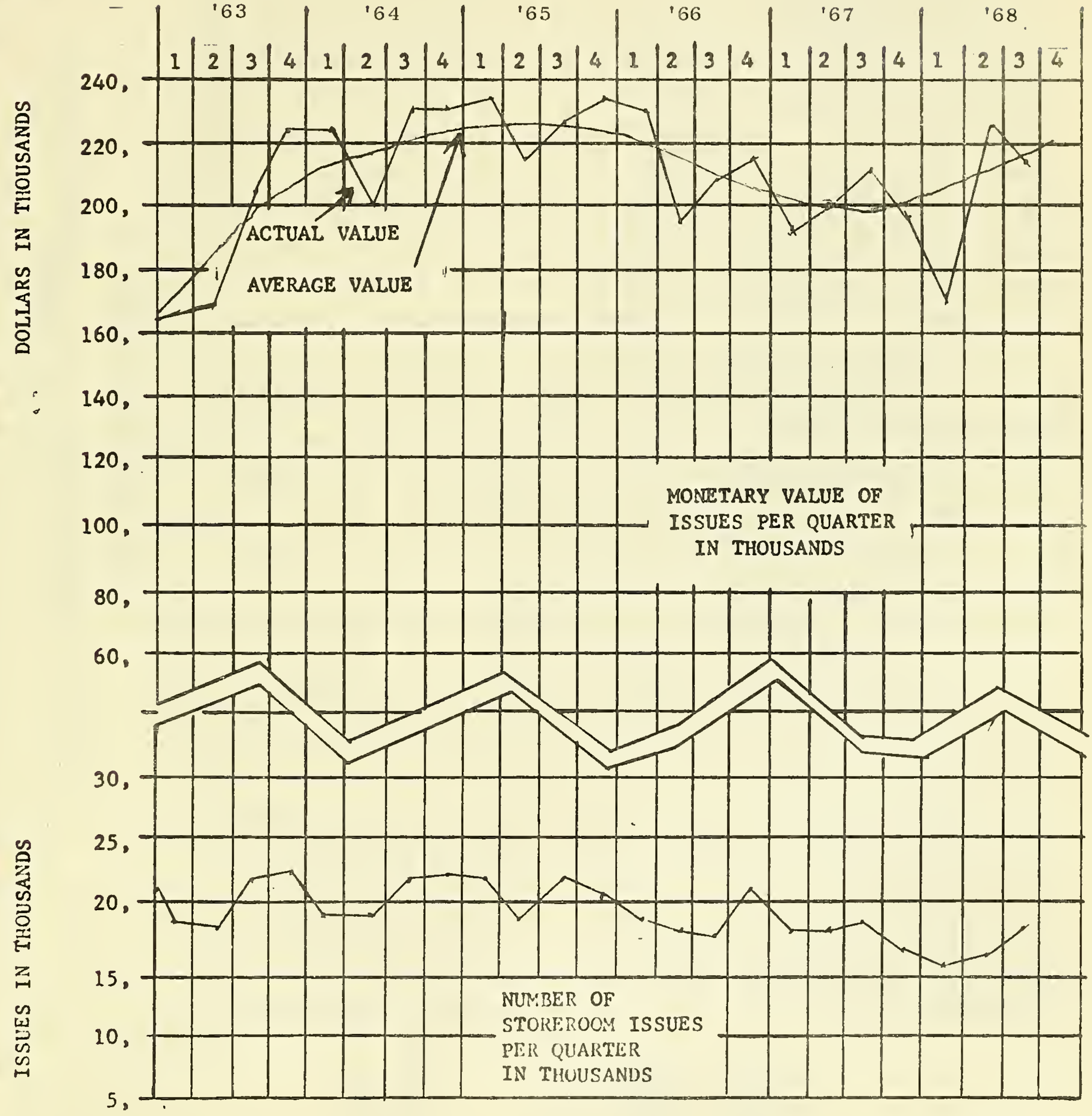


CHART I

NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH SERVICES - PLANT ENGINEERING BRANCH

SHOP WORK BACKLOG SUMMARY

Reporting Period **August 1965 thru December 1966**

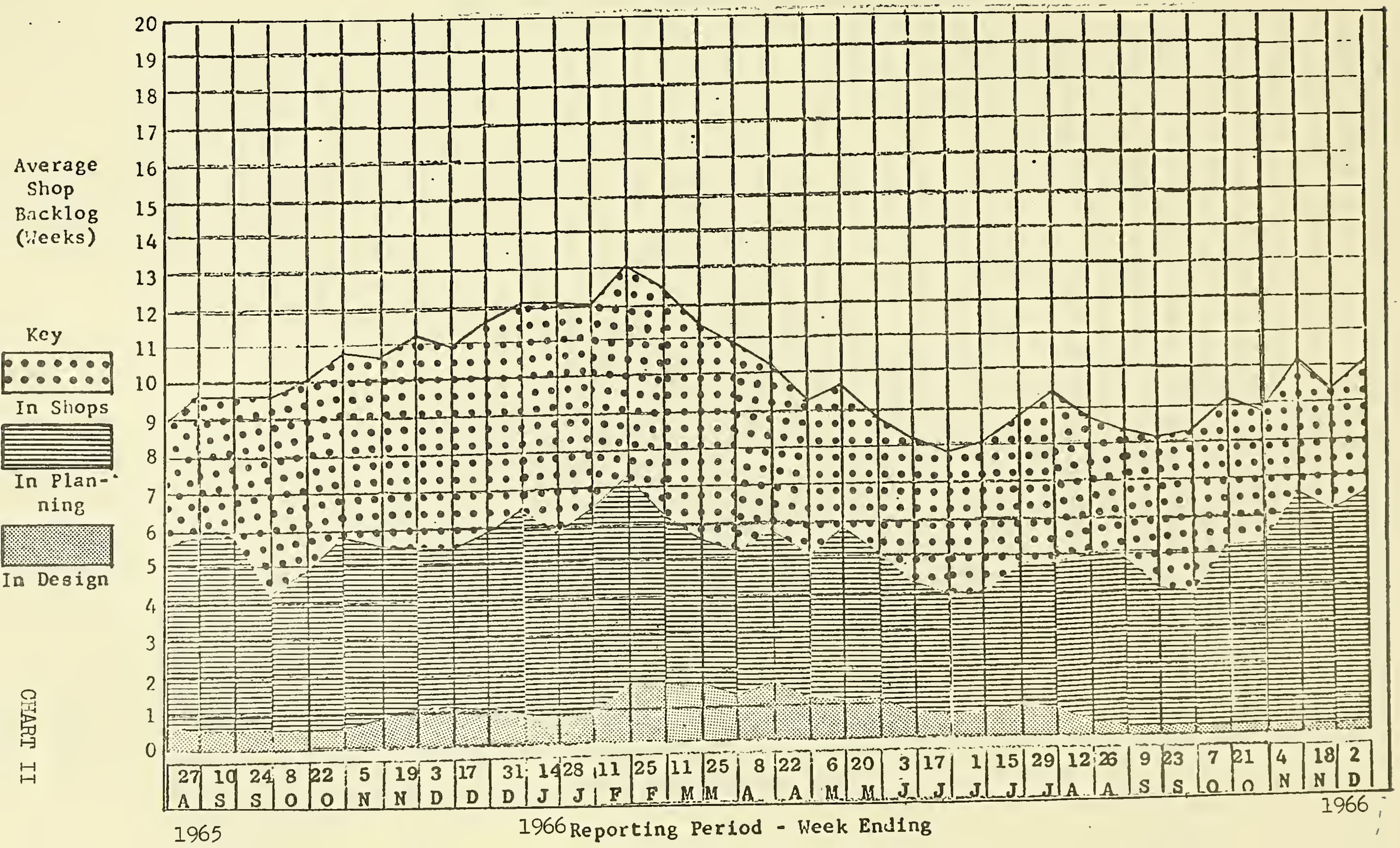


CHART II

NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH SERVICES - PLANT ENGINEERING BRANCH

SHOP WORK BACKLOG SUMMARY

Reporting Period **December 1966 thru March 1968**

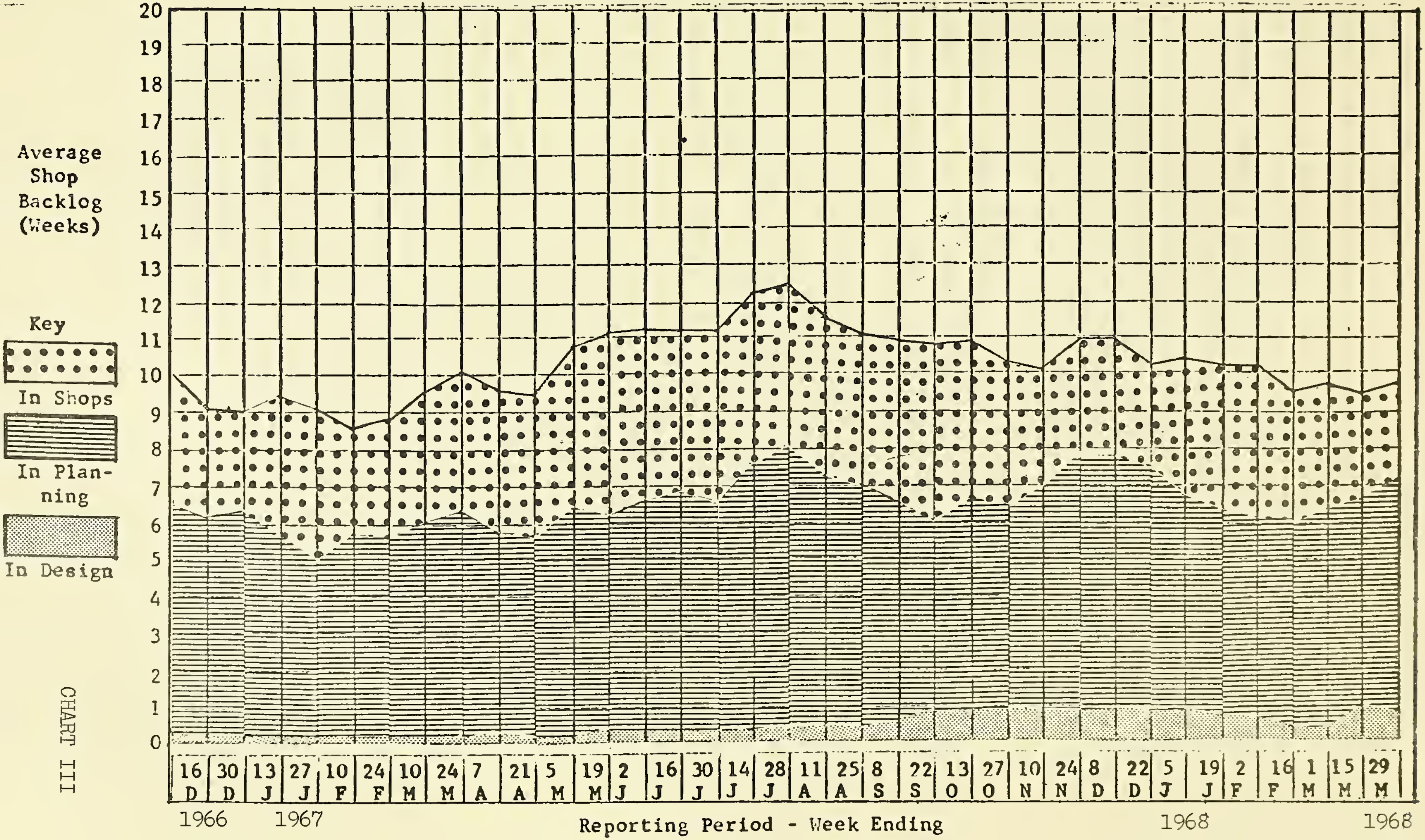


CHART III

with the Library being opened for use in April 1968.

Extension of Clinical Center Cafeteria

Contained in appropriations for both 1961 and 1964 was a total of $695,000 for the extension of the Clinical Center Cafeteria facilities. Essentially this project provides for increasing the seating capacity and separating patient food preparation from employee facilities, enabling the employee food service to be operated by an outside concessionaire, leaving specialized preparation of patient diets the sole concern of the Clinical Center dietetic department. The POR was completed in February 1964 and the design contract was awarded in July 1964 with design completed in November 1965. The construction contract was awarded in April 1966 and is expected to be completed in July 1968.

Expansion of Clinical Center Facilities

In 1966, $1,550,000 was provided for specific additions to the Clinical Center. The additions specified were a subbasement under the relocated NIH Library ($650,000) and two floors on the south half of Wing D ($900,000).

Both of these additions are scheduled for final completion by the end of this fiscal year with the Library space already occupied on the two top floors and the subbasement area being converted to use by the Medical Arts and Photography Branch. The Wing D Addition is substantially complete except for metal partitions and acceptance of the mechanical work in the 8th floor machine room.

Virus Isolation Facility, Building 41

Funds were provided the NCI in 1965 for the construction of a virus isolation facility which would provide an experimental research environment capable of handling all levels of hazardous work related to virus research.

Dr. Kenneth M. Endicott, Director, National Cancer Institute, NIH stated before a Subcommittee of the Committee on Appropriations, House of Representatives in February, 1965, that "The control and containment of biohazards is a newly recognized problem in cancer research. Only recently has it become apparent that certain viruses, heretofore thought to be species specific, can, in some cases, cross species lines, especially in the highly concentrated preparations (in some cases thousands of times beyond the normal state) required by laboratory experiments. This constitutes a definite hazard to personnel engaged in virus studies and to the success of their research should the materials with which they are working become contaminated".

Consequently an emergency program for construction was initiated by the NIH. A contract for design was awarded in November 1965, and the design was completed in May 1966. A construction contract in the amount of 3.2 million dollars was awarded in June 1966, and the building is scheduled for completion and beginning occupancy in July 1968.

Isotope Laboratory Addition

The 1967 Buildings and Facilities Appropriation included $500,000 for the design and construction of an extension to the existing Isotope Laboratory, Building 21. This additional space will include laboratories for the assay of radioactive materials, calibrating radiation survey instruments and for student use in the Radioisotope Training Course. This addition will also provide for an increase in the present office space.

The POR was completed in March 1967 and design was completed during April 1968. The construction contract is scheduled to be awarded in June 1968 with completion of this facility in July 1969.

Alterations For Direct Research Support: The trend of this service can be assessed by comparing annual expenditures for station labor materials and contract work for the past four years.

Station Labor Material

Fiscal Year	Material Expenditures (accrued)
1964	$486,200
1965	467,500
1966	500,000
1967	558,000
1968	543,000 **

Contract Expenditures (Awards)

Fiscal Year	No. of Contracts	Costs
1964	126	$659,500
1965	87	330,800
1966	77	727,000
1967	68	1,136,335 *
1968	85	800,000 **

* 1967 Includes renovation of Clinical Center 5th floor library area to laboratories ($450,000).

** Projected by estimate for 12 months. Actual expenditure for first nine months - Station Labor $406,722; Contract $205,000.

The above data shows that the level of services provided by station labor and by contract for alterations in direct support of research has remained fairly level during the past five years.

Engineering Design Services: During the report period, the engineering staff of the Branch conducted surveys and prepared plans and specifications for contracted work and for the more complex station labor projects. Professional services contractors were utilized as necessary, with the engineering staff directing and reviewing their efforts. The work of professional services contractors engaged by the Public Buildings Service, GSA, for the design of NIH facilities was also reviewed by this group.

This year a greater proportion of the engineering design work was performed by professional services contractors. This was largely due to late programming of fiscal year requirements by the Institutes, and restrictions imposed in the first several months of the year on contracting authority. This resulted in the major portion of the year's work being established after February 1, and the limited time remaining necessitated contracting much of the work.

A summary of the work for which design was completed during the report period follows (projected through June 1968):

Type	No. Completed	Actual or Estimated Cost of Construction
Professional Services Contract	16	$2,344,000
Staff Projects for Contract Work	94	1,515,000
Staff Projects for Shop Work	85	
Engineering Studies or Surveys	24	

A few of the more important projects are listed below:

Alterations

Renovate "C" Level Areas of Library, Building 38	$ 70,000
Prepare B2 Area of Library Addition for Medical Arts & Photography Work, Building 10	95,000
Remodel West End, 2nd and 3rd Floors, Building 10, NIMH	250,000
Modifications to Building 36, NIMH	250,000
Modifications to Building 37, NCI	900,000
Modifications to Building 5, NIAID	225,000

Plant Maintenance

Repaint Public Areas, Various Buildings	$ 30,000
Remodel Electrical Distribution Systems, Rocky Mountain Laboratory	75,000
Install Drainage System West of Building 14A	8,500
Resurfacing of Parking Areas, Reservation	35,000

R&I and New Construction

Extension to Building 21	$425,000
Stairwell Additions & Elevator Additions & Replacements, Buildings 2 and 3	300,000
Air Conditioning Modifications, Building 10	615,000

Joint Refuse Disposal Study: A study made by Metcalf and Eddy Engineers of Boston, Mass., has resulted in decisions to (a) build a joint-use facility to serve the incineration requirements of NIH, NNMC, and WRAMC, (b) construct this facility at the WRAMC Forest Glen Annex, and (c) have NIH act as the builder and operator of the facility. Completion of this facility is scheduled for the fall of 1970. During FY 1968 an additional study was completed by Metcalf and Eddy Engineers relative to collection and transporting methods and procedures for the various forms of NIH-generated refuse. This study also identified new transporting equipment to be procured, and special design features required in the new Incinerator Plant.

Work Procedures, MARU, Panama Canal Zone: Formal agreements are being arranged with the Panama Canal Company for design and construction efforts required to support facility alterations, maintenance and improvements needed by MARU. Procedural arrangements between DRS and NIAID have been developed to effectively execute work requirements utilizing the Panama Canal Co., with DRS acting as the agent of the Institute.

Power Plant: During the past year the operating efficiency of the boilers has increased approximately 4 percent over previous years, with a resultant fuel saving of approximately $22,000/year based on FY 1967 fuel usage. A number of factors, which are listed below, contributed to this:

1. Installation of shot cleaning system giving better heat transfer to preheated air. This also resulted in a manpower saving of approximately 500 manhours per year previously required to clean tubes.

2. Increased load.

3. Improved feedwater controls.

4. Steam atomizing burners.

5. Lining inside of boilers with additional insulation by the gunniting process.

6. Low sulphur fuel oil resulting in cleaner surfaces and better heat transfer.

7. Improved operating procedures.

A no-break electrical power system was installed for the boiler controls. With this system the boilers will continue to operate uninterrupted should an electrical power failure or a dip in voltage occur. The system consists basically of a bank of batteries and an inverter which continuously supplies alternating current to the boiler controls.

On February 12, 1968, an all-time steam peak of 261,000 lbs./hr. was reached in the boiler plant. This occurred with the outside temperature at about 20°F and with Buildings 36 and 37 taking a light load on the preheater coils. The buildings were maintained at about 55°F to 60°F during this period of construction.

The addition of a fourth boiler in the power plant brought the steaming capacity to 600,000 lbs./hr. Also, a new air conditioning plant brought its capacity to almost 20,000 tons, thus making it one of the largest in the country. The technical and administrative responsibility, therefore, increased, making it necessary to strengthen the supervision in the plant. The positions of Power Plant Superintendent and Assistant Superintendent were established and filled by a professional mechanical engineer and a mechanical engineering technician. Also, because of the increased plant size and increased responsibility and plant importance, the position of Shift Superintendent was established and filled, thus allowing the Shift Head to spend full time supervising and overseeing the operation of this large, important facility.

Surveys: Many facets of the utilities systems have been studied for improved performance and appropriate action planned or placed into effect. For example: improvements in air quality in the building environments is being obtained by establishing better tests to determine whether the filter media meets performance requirements, and by replacing outdated filtration systems; oil carry-over into the central compressed air system will be reduced by improving on filters and maintenance of filters; a conveyor system being installed in the Incinerator Plant will enable more effective handling of potentially hazardous and normal wastes received in GI cans; a twice yearly schedule of engineering inspection trips has been adopted for MARU, Panama Canal Zone, and the Rocky Mountain Laboratory to identify potential plant and utility system deficiencies.

Interim Facilities, Research Triangle Park, N. C.: A second phase of interim facilities for DEHS is in the early design stage. This will include a laboratory building, an aerotoxicology building, an experimental animal building, and a central utilities plant. The structures are to be constructed with a build-lease contract, with construction expected to start approximately January 1969.

Incinerator: Formerly, fairly large quantities of scrap lumber items were delivered to the incinerator for disposal. These were bothersome to the burning crew, frequently requiring cutting and sawing before being charged into the burning chambers, and also causing considerable damage to the fireclay brick linings. A study showed that a substantial part of the material, wooden shipping pallets, and skids, would be taken by GSA and GPO where, apparently, many of them originated. Arrangements were made to collect them for pickup. These procedures resulted in a saving estimated at $800 to $1000 per year, as well as reduced breakage of brick work.

Maintenance of Water Stills and Autoclaves: Several years ago, loss of skilled personnel through retirements, transfers, etc., resulted in a critical shortage of personnel skilled in the operation and maintenance of water stills and autoclaves. The quality of distilled water in the house systems was being affected, and numerous complaints were received regarding malfunctioning of autoclaves. Near the end of FY 1967, all maintenance to these kinds of equipment was centered in a trained crew especially selected for this work. During the first year of this arrangement a marked improvement was noted in the quantity and quality of distilled water available in the buildings, and the trouble calls on autoclaves were reduced to only a fraction of those formerly received.

Painting Schedules: As an economy measure, the maintenance repainting schedule for laboratories and offices was increased during the year from six to seven years, and from three to four years in nursing units of the Clinical Center.

Elevators: All of the elevators on the reservation, except those in the newest buildings still under builder's responsibility, were brought under formal preventive maintenance procedures under which PM inspections are made to uncover deficiencies, hopefully to prevent breakdowns. This does not apply to elevators in Buildings 10 and 31, which are maintained by contract.

Completion of Major Projects: Several major construction projects were carried through to completion during the year, as follows:

Project	Accepted for Beneficial Occupancy
Library Addition to Clinical Center	March 8, 1968
Cafeteria Addition to Clinical Center	Accepted for partial occupancy January 26, 1968

Laboratory Refrigerators: The first two shipments of 50 each of an improved model undercounter laboratory refrigerator were received and are carried as stock items under the shop stores system. The refrigerators are single-temperature (no freezer compartment), six-foot capacity, sized to be compatible with standard laboratory furniture and having an explosion-proof interior and other safety features.

Ultra-low Temperature Freezers: In recent years there has been a great amount of administrative confusion and technical difficulty in obtaining warranty repairs on ultra-low temperature freezers. Arrangements were worked out with the Supply Management Branch under which PEB is to be the sole contact point for requesting freezer repairs, both during and after the warranty periods. Maintenance history and cost records will be maintained to use in evaluating reliability of the various manufacturers' models.

Electrical Outlets in Corridors: In collaboration with the NIH Safety Office, standard details were developed for providing adequate load protection for electrical outlets supplying power to laboratory equipment permitted to remain in corridors.

Freezers in Building 10: The Branch assisted OD in surveying the requirements for freezer space in the Clinical Center, which resulted in a program being approved which allows a limited number of freezers to be permitted in corridors and freight elevator lobbies. Suitable space was also made available and provided with electrical power for long-term freezer storage on the third floor of Building 14A for many of the freezers which could not be accommodated in Building 10.

Organization: The Grounds Maintenance and Landscaping Section was reorganized slightly during the year. The reorganization consisted mainly of redefining functions and consolidation of the former Pavement Maintenance Unit with the Heavy Equipment Unit. A landscape architectural draftsman was hired to assist in development of master landscaping plans to be implemented when completion of major construction projects will permit. The master plans, covering both the main reservation in Bethesda and NIHAC, are expected to be completed by July 1968.

With the completion nearing for Buildings 35, 36 and 37, a satellite unit of building engineers was established under the South Buildings Unit to handle the operation and minor maintenance of utility systems in these buildings. The group operates out of quarters in Building 37 to obtain greater productivity of manpower.

NIHAC Grounds: Early in the year a shelter belt of coniferous evergreens was planted at NIHAC by contract along Elmer School and Club Hollow Roads. Several losses occurred during the winter. The plants concerned are covered by maintenance and warranty clauses of the contract and will be replaced by the contractor.

Employee-Management Relations: During FY 1967, the Washington Area Metal Trades Council, AFL-CIO was given exclusive recognition for a second bargaining unit--all wage board employees of the Shops Section. The Council previously had been recognized for the Grounds Maintenance & Landscaping Section, and a formal agreement was negotiated several years ago. Negotiations for the Shops Section agreement were completed on April 18, 1968. The Council has indicated its desire to renegotiate several sections of the Grounds Maintenance agreement, particularly those clauses dealing with training and promotions. The negotiations are expected to be completed by the end of the fiscal year.

Training: The Branch supported approximately 550 man-days of formal training in FY 1968, or roughly one man-day per employee. A total of 128 individuals, or 22 percent of the total work force, participated in the training.

In-service and interagency training accounted for 446 man-days, consisting primarily of a formal refrigeration and air conditioning course taught within the Branch, and a newly inaugurated series of courses conducted by the staff of the Grounds Maintenance and Landscaping Section. The first of these, entitled "Plant Life," is being attended by 27 individuals. Also notable are a course for first-line supervisors, conducted by a psychiatrist from NIMH, and a course conducted for the Branch by the Montgomery County Board of Education, aimed at providing basic education to prepare employees having a minimum formal education for the journeyman helper's examination.

Non-government training accounted for 110 man-days, including ICS correspondence courses, courses for professional engineers, training in refrigeration and air conditioning controls, specialized training on turf grasses, etc.

D. Problems

Incinerator: In FY 1967 new Rotoclone exhaust gas scrubbers were installed in the incinerator plant to eliminate the release of fly ash and other particles into the atmosphere. Basically, the scrubbers perform satisfactorily for their intended purpose, but major maintenance problems have arisen which were not foreseen either by the NIH staff or consultants retained to design the system. Because of the high acidity of the effluent, there has been considerable corrosion to waste lines and scrubber components, requiring replacement. Efforts are under way to determine the requirements to keep the units in operation until the new incinerator is constructed and operational, at which time the present incinerator is to be abandoned. These problems may be typical of what may be expected under impact of the air pollution control program when applied to incinerators of similar size and design operated by state, county, and local governments, as well as by private industrial firms.

Grounds: The general condition of the grounds leaves much to be desired. The large amount of trenching and building construction, with the accompanying stock-piles of supplies, materials, and debris, has kept a major part of the campus in an "eyesore" condition for the past year. GML has expended much labor attempting to save valuable materials by transplanting trees and shrubbery from construction areas to other areas. Many more hours were spent giving special attention to large trees remaining within construction areas, in an effort to preserve these valuable assets weakened by grade and water table changes, physical abuse, and a very dry winter.

During a good part of the year, GML had to operate with a reduced supervisory staff and shortages in other categories. Under these conditions the plan, to take "first things first", resulted in having to forego the customary "polish" in undisturbed areas, the usual mark of well-kept grounds.

Uniforms: When Government-furnished uniforms first were provided for PEB wage board employees about eighteen months ago, a few employees were found to have skin sensitivities to them. At first this was believed to be caused by washing procedures but later was traced to some agent in the cloth. During FY 1968, new uniforms were obtained for employees experiencing irritation. Replacements will all be of the new type. Evidence to date indicates that the new materials do not cause skin irritation.

Safety Shoes: For several years the Branch, in cooperation with the NIH Safety Office, has been trying to establish a safety shoe program, a simple and inexpensive means for employees to buy safety shoes and be properly fitted at NIH. Several administrative difficulties have prevented going ahead with this program but interim arrangements have been made with one manufacturer to provide samples. During the past several months an appreciable number of employees have ordered safety shoes, and those received have been highly satisfactory.

Master Utility Extension Contract: During the year the project to extend underground steam and chilled water lines has required extensive trenching operations. Where the trenches have run near the older buildings, considerable problems typical of this type construction have developed. Breaks in cables supplying street lighting circuits have been almost a daily occurrence, and some street lighting circuits were out of service for extended periods of time. Other major utility interruptions were as follows:

(a) On July 28, 1967, the contractor broke an 8-inch water line located east of Building 3, which affected Buildings 3 and 21. Station forces isolated the break and pumped out the trench so the contractor could make the repair. About 4 inches of water flooded the east basement of Building 3, but no serious damage to equipment occurred.

(b) In October, the contractor broke a gas line to Building 9 while excavating the steam trench in Parking Lot IB behind Building 1. Gas service to the building was secured for one and one-half days while repairs were made.

(c) On January 30, 1968, the concrete encasement housing high voltage feeders 1, 14, 33, and 42 across an open ditch over the new steam line at the northeast corner of Building 3 collapsed. The weight of the concrete put a strain on these cables which supplied power to Buildings 3, 7, 8, 9, 12, and 16. To avoid the possibility of a cable failure which could have caused loss of power to these buildings for an extended period, power through the cables was shut off for a period of about 8 hours while the concrete encasement was removed and the strain on the cables relieved. During this time the above buildings were partially supplied with emergency power from gasoline and diesel generators. During the next two weeks the cables were replaced, one at a time, without any power outage to any of the buildings.

(d) On March 26, 1968, while excavating around the thrust block on the chilled water line east of Building 12A, the contractor broke a vent line. Quick action by Power Plant personnel in closing the 20-inch chilled water valves to this section of the line prevented a large loss of water from the chilled water system.

Personnel Levels: Some difficulties were experienced during the year in recruiting skilled personnel to fill vacancies. The problem was complicated by several "freeze" periods when new employees could not be hired. Recruiting efforts were stepped up in the third and fourth quarters, and it is expected that the year will end with most of the critical needs filled.

As of April 30, 1968, there were on board 570 employees, an increase of 31 over the 539 who were on board on July 1, 1967. During this period, 75 new personnel came on board, and 44 were lost through deaths, transfers, retirements, resignations, etc.

The comparative on-board figures, by section are as follows:

July - 1967		May - 1968	
O/C	12	O/C	12
EDS	28	EDS	29
GMLS	47	GMLS	50
PCS	32	PCS	31
Constr.	13	Constr.	13
MES	234	MES	262
Shops	173	Shops	173
Total	539	Total	570
Shop Stores	21	Shop Stores	25

E. Program Plans

Operating Plans: Long- and short-range plans used to direct the day-to-day business of the Branch include: (a) operating budget and related reports; (b) daily reports from the preventive maintenance system as needed to generate the maintenance needs requiring immediate attention, and monthly and annual reports for major repair and improvement program plans; (c) weekly workload reports which reflect the estimated craft labor requirements by trade; (d) monthly workload reports which reflect the estimated engineering manpower requirements for engineering services by discipline; (e) weekly personnel status reports which report the available manpower by organizational unit resulting from personnel attrition and recruitment; and (f) monthly Shop Stores status reports.

F. Publications

A feature article prepared by a planner of the Grounds Maintenance and Landscaping Section was published in a nationally-distributed periodical:

> Rosenkranz, George P.: Midwinter Weed Control--
> useful practice for National Institutes of Health.
> Weeds, Trees and Turf - 6: 18-19, Oct. 1967

Summary of Branch Activities July 1, 1967, through June 30, 1968

LABORATORY AIDS BRANCH Dr. R. D. Zinn, Chief

I. SUMMARY

The Laboratory Aids Branch constitutes a basic central research resource of fundamental importance to the intramural research programs of the National Institutes of Health. Its responsibilities include producing genetically characterized research animals and animals of known microbial flora and health status; procuring, conditioning, and issuing animals obtained from outside sources; animal surgery, X-ray, and recovery; animal disease diagnosis and control; maintaining animals and collecting biological specimens; preparing bacteriologic and tissue culture media, tissue culture cells, and laboratory glassware; and providing professional services relative to animal procurement, health, care, and husbandry. Additionally, the Branch is responsible for conducting studies necessary to advancing the definition of experimental animals, their health, and optimum maintenance.

Major emphasis was placed upon data processing of production and animal issue information in order to achieve greater efficiency in the utilization of limited production facilities. Additional efforts were made to establish more meaningful communications with the Institutes and Divisions regarding their current and future requirements for experimental animals. Efforts to improve the quality of all animals furnished to intramural research programs were continued and intensified. For the first year in recent history, the rodent and rabbit production colonies experienced no major outbreaks of disease. Significant improvements in the quality of the random source dogs and cats issued were noted and are directly attributable to the lengthening of the conditioning period from 30 to 45 days.

A development of singular importance, the successful establishment of a large colony of donor dogs to furnish whole blood, has resulted in a significant reduction in the numbers of dogs required for research purposes at NIH. The furnishing of blood, coupled with improvements in the health status of conditioned random source dogs, reduced the needs for dogs by 786 animals. Projected dog issues for the year will be 3,612, the fewest number of dogs issued since FY 1960.

II. BRANCH PROGRAMS

Production of Laboratory Rodents and Rabbits

A. Objectives

To support biomedical research at NIH by providing quality rodents and rabbits of uniform genetic and health characteristics. To advance the definition of what constitutes satisfactory experimental rodents and rabbits.

B. Current Programs

1. Production Program

Major emphasis was placed on data processing of production and animal issue information in order to achieve greater efficiency in the utilization of limited production facilities. Additional efforts were made to establish more meaningful communications with the Institutes and Divisions regarding their current and future requirements for experimental animals.

2. Genetics Program

This program is designed to maintain the genetic integrity and desired features of the foundation inbred strains of mice, rats, and guinea pigs; and to support the production effort by providing genetically controlled breeding stock for the production colonies.

C. Program Progress and Accomplishments

Production and issue of rodents and rabbits was at the maximum permissible level consistent with adequate housing of animals within the limited production facilities which are available. Improvements in management and care practices resulted in a production year free of any major disease outbreak.

An intensified program of nutrition research was initiated through the addition of a staff nutritionist and the establishment of a nutrition laboratory. Efforts will continue to more specifically define the dietary requirements of the several species maintained and produced in order to eliminate the necessity for feeding a variety of vegetable supplements. Some progress was made in this regard, and all supplements have been discontinued for the mice and rat production colonies. More rigid inspection and disinfecting procedures have been continued for the supplements being fed to the guinea pig and hamster colonies.

Updating and improvements to caging systems have been continued, and new and improved caging, including those with filter tops, are under continuing evaluation.

Disposable waste receptacles are now utilized in all rat and mouse rooms. Use of these containers eliminates the necessity for having GI cans in the rooms and precludes the introduction of foreign microorganisms through improperly cleaned GI cans.

D. Problems

Existing and anticipated demands for animals in the face of limited production capacity causes real doubt about the availability of animals for research needs in the immediate future. Production facilities approved for the Animal Center under Phase II were reduced by 50 percent, and the remaining portion is still some six years away. During this same period, available laboratory space will be increased by some 40 percent.

E. Program Plans

Hopefully, the production space presently occupied by the Division of Biologics Standards in Building 14D and the production rooms occupied by the National Cancer Institute in Building 14E will be returned to the Laboratory Aids Branch for programming and utilization as rodent and rabbit production facilities. Return of this space will permit an estimated increase of 15 percent in our production capabilities. A small isolation facility for housing new rodent and rabbit foundation stocks and strains has been requested for FY 1969 at the Animal Center. This facility is urgently needed for meeting requests for establishing and producing new strains and stocks to meet specific research requirements. All incoming strains and stocks will be isolated for three generations in this facility, to preclude the introduction of diseases into our production colonies.

The installation of a new vacuum exhaust system on the Building 14A cagewash and the improvement of the existing vacuum system on the Building 14F cagewash during FY 1969 will permit a significant improvement in cage cleaning practices. When operational, these vacuum systems at the cagewashers will eliminate the practice of dumping soiled bedding from animal cages within the production rooms. This will decrease the dust level in the animal rooms and allow personnel to give more direct attention and time to the animals.

Production of Special Animals

A. Objectives

To furnish intramural research programs with laboratory animals whose associated flora and fauna is defined in some specific manner, i.e., germfree, pathogen-free, RIF-free, etc. To develop systems and methods for more efficient production and use of a greater variety of these animals.

B. Current Programs

Four strains of germfree mice and four strains of germfree rats are being produced in stainless steel and flexible plastic isolators. One additional strain of mice and three additional strains of rats were introduced into the barrier rooms during the past year. A total of five strains of mice and four strains of rats are now maintained and produced in the SPF state.

Work is continuing in an effort to establish the hamster in the germfree state. Initial work is also underway to gain experience with the germfree cat and rabbit. A modest program was undertaken during the year to establish the Hartley guinea pig in the SPF state. Our work to date has been somewhat encouraging, and 30 guinea pigs are now in the SPF state. This work will be continued and, when satisfactory procedures are established, a group of Strain 13 inbred guinea pigs will be introduced into the SPF barrier in order to provide greater health security to this strain.

C. Program Progress and Accomplishments

The flexible plastic isolators for housing the RIF-free chickens have been placed in full operation in the Building 14G facility. They have proven satisfactory, and no contamination problems have been experienced. Additional caging for rats and mice is on order, and when received and operational, will permit a higher level of utilization of the Building 14G SPF facility.

D. Problems

A further delay was experienced in getting the new RIF-free chicken facility operational at the Animal Center. Partial occupancy was achieved during the year, and full production should be achieved during FY 1969.

Success in establishing the hamster in the germfree state continues to be delayed, though ultimate success is expected. Enlarged cecum syndrome continues to be a problem with guinea pigs in both the germfree and SPF states.

E. Program Plans

Development work will be expanded to include more intensive efforts with the cat and rabbit. The work with the hamster and guinea pig will be continued. Additional strains of rats and mice will be introduced into the germfree and SPF state in order to gain production data prior to the construction and occupancy of the Phase II SPF rodent facility.

Production of Laboratory Carnivores and Canine Blood

A. Objectives

To produce laboratory cats and dogs of defined characteristics to meet intramural research requirements. To reduce the overall needs for dogs by supplying blood from a canine donor colony.

B. Current Programs

The canine blood donor colony, which was established in July 1966, has been expanded from the original 25 dogs to 113 dogs, with a production capacity of 158 units of blood per month. The laboratories which have been using blood from these animals have been enthusiastic in their acceptance of it. The current short-term objective is to expand the colony to about 200 dogs, which is equivalent to conditioning 140 dogs for issue each month. Expansion involves the addition of new dogs to the colony and replacement of those which have undesirable characteristics. The source of replacements is the breeding colony maintained at Building T-8. Dogs comprising the blood donor colony are being selected for uniformly large size, good temperament, and A negative blood group.

The original breeding colony of white hounds has been largely replaced by American foxhounds. The breeding program is confined to production and intensive selection of dogs to improve the genetic characteristics of the colony. A significant number of the dogs produced serve as additions and replacements for the blood donor colony.

Three English foxhounds were added to the colony, and limited matings have been made. A small number of dogs of this breed are maintained as a nucleus from which to expand. Thirteen inbred beagles were also introduced into the colony.

The contract for rearing American foxhounds was renewed. The breeding level originally planned, 100 females, will be achieved in FY 1969. Production is expected to achieve 400 research dogs during the current contract year.

The cat breeding colony consists of about 30 breeding females. Cats are subject to intensive culling procedures in order to establish a high producing colony with uniform characteristics. Substantial progress has been made in attaining this goal.

C. Program Progress and Accomplishments

Blood issues will be approximately 850 units for the year (=425 dogs). The number of puppies produced is expected to be about 390, and kittens, 140.

Renovations in Building T-8 were completed this year, resulting in increased and improved personnel, laboratory, office, and storage space. The acquisition of adequate laboratory equipment and personnel this year will permit more in-depth studies to be made on the dogs and cats maintained in the colony.

D. Problems

The beagles, American and English foxhounds represent the full range of dog sizes required for research use. Production of meaningful numbers of dogs for this purpose, however, is not possible in the temporary facilities available. Likewise, the cat colony cannot be expanded. The blood donor colony can be increased to within 66 percent of its projected size.

E. Program Plans

Additional facilities have been requested in which to house the dog and cat breeding colonies and the canine blood donors. In such a facility, about 2,200 puppies could be reared yearly, and the blood equivalent of 2,500 dogs could be produced. Combined with the foxhounds expected from the contract source, such an in-house breeding and donor program would provide the NIH with 5,500 dogs annually. These facilities would also permit the rearing of 1,500 to 2,000 kittens per year.

Studies are in preparation which are designed to provide more definitive characterization of the dogs and cats reared in the colonies. Work is also in progress to determine objectively some of the environmental and psychological requirements of dogs maintained in confinement. A quality control program is being developed to insure the production and issue of normal canine blood on a continuing basis.

Quarantine and Conditioned Animals

A. Objectives

To provide intramural research programs, insofar as possible, healthy random source dogs, cats, primates, and feral animals.

B. Current Programs

The program consists of controlled quarantine and conditioning procedures including the application of clinical veterinary medicine. Preventive medicine programs and the application of sound husbandry practices constitute the core of the program. The flow of animals to the laboratories was partially interrupted twice in the report year--one period of two weeks for dogs, and a four-week period for cats--due to the failure of animal suppliers to deliver animals in requested quantities. However, at no time was any investigator totally denied research subjects. Daily populations of all species were maintained at the highest possible level, consistent with facility utilization and the availability of animals from suppliers.

C. Program Progress and Accomplishments

This is the first full report year under the conditions imposed by the Animal Welfare Act. The effects of the Act upon the conditioning program were minimal. Previously implemented procedures permitted compliance with the law without major changes or loss of function. The purchase price of dogs and cats increased significantly. The general quality of the animals and the numbers offered for sale declined slightly. Monthly morbidity and mortality figures did not change appreciably.

A full year of experience with a 45-day conditioning period for dogs and cats was completed. The health and general body condition of 45-day conditioned animals is clearly superior to previously issued 30-day conditioned animals. The conditioning programs for subhuman primates were carried out without major change from previous years. The trend toward the utilization of chimpanzees and other large species continues, and imposes a further strain on our limited facilities.

Random source dog issues for the year are projected to 3,612. This represents the fewest dogs issued since FY 1960, when 3,443 dogs were issued. The sharp reduction during FY 1968 is of singular significance and may be attributed to the canine blood donor program which was initiated in July 1966. Eight hundred fifty units of normal whole blood were issued during FY 1968 and represented a net savings of 425 dogs. Additional savings in the numbers of dogs issued may be attributed to the improvement in quality which resulted from the 45-day conditioning period. Cats and primates were issued at approximately the same rates as in FY 1967.

The increased conditioning period for random source dogs and cats has brought about significant improvements in the physical condition of the animals at the time of issue. While the total effect of previous disease experience cannot be corrected, the animals are in a more balanced nutritional state and their physiologic values fall more nearly within acceptable limits.

D. Problems

Continuing delay in the design and construction of the new primate facility for the Animal Center prevents development of expanded primate quarantine and breeding programs.

Animal Health

A. Objectives

To characterize and improve the health status and to study the naturally occurring diseases of laboratory animals produced, quarantined, or utilized in biomedical research at the National Institutes of Health.

B. Current Programs

Disease control in closed colonies of rodents and rabbits is achieved through a multi-disciplined approach to monitoring. Pathologists and microbiologists work closely with production personnel to identify, control, and eliminate diseases. Diagnostic service is also provided to other program areas of the Branch.

Routine control of infectious diseases of primates is approached through a program of tuberculin testing, bacteriologic monitoring, and treatment of clinically affected animals with drugs and antibiotics. Control of infectious diseases of dogs and cats is carried out through a program of routine immunization and by treatment of clinically affected animals with drugs and antibiotics. Health of ungulates is maintained through a program of preventive medicine, routine testing, and clinical veterinary medicine.

A nutritionist was added to the Branch staff during the year. A nutrition laboratory was established to deal with the nutritional problems of laboratory animals.

C. Program Progress and Accomplishments

For the first time in recent years, the production colonies suffered no major disease outbreaks.

Salmonellosis has not recurred in the guinea pig colonies since the feeding of kale was discontinued in late 1966. The data at that time indicated that kale contaminated by poultry manure had been the source of previous infections. Cabbage washed in chlorine solution with the outer leaves discarded was substituted for kale.

The results of current feeding trials indicate that commercial rations have improved, and it may be possible to omit supplemental feeding of leafy green vegetables to guinea pigs. Autoclaved hay appears to be satisfactory for the purpose of supplying bulk.

The composite sample test for coccidiosis again proved to be effective. Coccidiosis was detected in two cages in one rabbit room in January 1968 and was quickly eradicated.

Fulminant hemorrhagic pneumonia, caused by *Streptococcus zooepidemicus*, has continued to kill approximately 4 percent of newly purchased dogs. Although the causative agent has been found to be sensitive to high concentrations of furacin *in vitro*, the duration of the disease is generally too short for effective therapy to be instituted.

The incidence of intestinal parasitism in newly purchased dogs was determined during a 7-week period. The examination of fecal specimens revealed nematode infestations, primarily hookworms, in 84 percent of the dogs. The incidence was 91 percent in dogs from Virginia and North Carolina and 71 percent in dogs from Michigan and Ohio. A new anthelmintic (trade name "Task"), was tested and found to be only 58 percent effective as compared to 100 percent effectiveness reported in recent literature.

Mortality in the cat conditioning colony decreased to a new low of 7 percent. The decrease is believed to have been brought about by stopping the use of phenolic disinfectants in the rooms and stopping the feeding of canned diets high in fish content (low in thiamine).

The overall quality and appearance of conditioned random source dogs and cats have improved greatly as a result of extending the conditioning period from 30 to 45 days.

Caseous lymphadenitis in goats, first diagnosed in 1966, has occurred sporadically but, in each instance, has responded satisfactorily to antibiotic therapy.

Attempts to isolate a virus from tissues of monkeys with sloughed-out buccal pouches were unsuccessful. As in the past, this poorly understood disease affected relatively few animals.

Another peculiar and difficult-to-identify bacterium has been isolated from rats in one of the barrier rooms. The biochemical identification has been confirmed by CDC as "aberrant *Citrobacter sp*." with serologic relationship to the Arizona group of organisms. Both *Citrobacter* and Arizona organisms are considered at times to be pathogens. No disease has been attributed to the agent in the barrier room.

D. Problems

Attempts to fill vacancies for a veterinary pathologist and a veterinary clinical pathologist have been unsuccessful, due primarily to our inability to meet salary requirements for specialists in these categories.

E. Program Plans

Ongoing programs outlined above will continue.

Special and Consultative Services

A. Objectives

Special services pertaining to programs requiring the use of animals and animal facilities are provided to Institutes and Divisions on a continuing basis. These include consulting on animal problems, issuing health certificates, furnishing surgical and X-ray services, and producing and issuing blood and blood products.

B. Current Programs

Veterinarians and other professional personnel furnish NIH investigators with information and advice concerning animal anatomy, physiology, genetics, husbandry practices, and disease problems. They also give advice regarding appropriate selection of animals for experimental procedures.

Outside inquiries on animal programs and facilities are also answered. Extensive time is devoted to visitors from all parts of the United States and abroad who have specific problems and questions regarding animal facilities and care. Staff members participate in the review of plans for construction and renovation of animal facilities for our own programs and provide similar consultative services to the Institutes and Divisions.

Surgical and radiological services are provided the Institutes and Divisions, including postoperative and long-term care for animals. Limited space and service is also available for radioisotopic procedures. Assistance and facilities are provided for acute experimentation and for the collection of metabolic by-products and body fluids from animals.

C. Program Progress and Accomplishments

The Building 28 experimental surgery and X-ray facilities are operating at the same level as last year. Considerably more activity is occurring in the long-term holding of dogs; this facility is at maximum capacity. Up-dating and sophistication of equipment and techniques in the surgery and post-operative areas continue.

Requests for large animals (ungulates) have increased.

Installation of an X-ray unit in Building 100 at the Animal Center will be completed during FY 1969. This will make facilities available to NIH investigators for radiography of large (farm-type) animals for the first time. Increased numbers of experimental surgery procedures were performed in the ungulate facility at the Animal Center.

The RIF-free chicken isolator building at the Animal Center was completed. Establishment of this flock will provide additional security and increased production of RIF-free eggs.

D. Problems

Facilities are inadequate or lacking for radioisotope and infectious disease work, housing of primates postoperatively and on a long-term basis, and housing of exotic species. Additional space for ungulates is needed and funds for making additions to Building 100 have been requested.

E. Program Plans

The Branch is continuing a comprehensive consultation program to assist the Institutes and Divisions in all areas of animal care and disease control. Existing activities in these areas will be further consolidated, and the program more adequately staffed to give NIH an organized and uniform program of animal care. An expanded training program for animal caretaker personnel will be initiated in September 1968.

Media Production

A. Objectives

To produce and issue high quality bacteriological and tissue culture media and tissue culture cells under controlled conditions. To furnish consultative services to the Institutes on related matters.

B. Current Programs

Media production is programmed to meet Institute and Division requirements for standard and special media that cannot be economically or satisfactorily obtained from commercial sources. Tissue culture cell production is aimed at supplementing Institute requirements not met by commercial contracting or individual laboratory preparation. Automated equipment is utilized wherever possible.

The quality control program for media and cell production was improved this year by the addition of sterility testing of each order of tissue culture media. These additional quality control tests are proving quite satisfactory in preventing contaminated media from being delivered to the investigators.

The overall demand for tissue culture cells increased sharply this year, and the liquid nitrogen cell bank service underwent further expansion.

C. Program Progress and Accomplishments

Requisitions processed this year leveled off after a sharp upturn in FY 1967. Bacteriological and tissue culture media also leveled off after a sharp upturn in FY 1967. Requests for bacteriological plates was down slightly from FY 1967. The production of tissue culture cells was up sharply over FY 1967, and this service continues to be in great demand.

D. Problems

The Media Unit continues to suffer from the inadequacies and limitations of its existing production space. The present area has been modified to the limits possible and automation substituted wherever feasible. In view of the fact that the Unit is producing at near maximum levels, it cannot be expected that requirements imposed by the occupancy of laboratories presently under construction can be met by the existing production capacity.

E. Program Plans

A Program of Requirements for an expanded and improved media and tissue culture cell production facility is under development. Every effort will be made to point out the extreme necessity for relocating the media unit into more adequate space.

Glassware Preparation

A. Objectives

To furnish NIH investigators laboratory glassware of the highest quality by processing through the steps of decontamination, sorting, cleaning, inspecting, plugging, wrapping, sterilizing and issuing. This overall operation includes processing of used glassware from the investigators and the introduction of new glassware from replacement stock.

To furnish consultative services on problems associated with laboratory glassware.

To furnish cagewashing services to the Clinical Center, Auburn Building, and Patuxent River Laboratory. To furnish ethylene oxide gas sterilization for heat labile patient and laboratory equipment from the Clinical Center and other Institutes and Divisions, upon request.

B. Current Programs

In addition to filling Institutes' demands for the volume and types of glassware, the Unit evaluates management and technical methods and equipment for improving the quality and maintaining the volume of issued glassware.

The cagewashing unit furnishes the services cited under A and studies problems associated with corrosion, scaling, etc. Washing the rubber backed carpets for the Clinical Center is still continued, and from reports received, this is the best way found to clean them.

C. Program Progress and Accomplishments

Glassware issues to the contributing Institutes and Divisions increased slightly over FY 1967.

The 18 by 150 mm disposable culture tubes used in fraction collectors were added to the Glassware Unit's stock and, at the present time, issues are running about 20,000 monthly.

The installation of new pump screens in the M-2 glasswashing machine has cut maintenance time 80 percent.

D. Problems

As in previous years, the Unit has continued to have a problem in meeting the daily demands for glassware trays for return of dirty glassware, as well as storage baskets.

A problem in locating more than one source for the special paper to be used for the automatic pipette wrapping machine has delayed completion of this project.

E. Program Plans

A prototype cardboard carton has been found and tested for the sterilization and shipment of petri dishes. This will replace wire baskets which were previously used for this purpose. It is hoped that the cardboard box will eliminate most of the breakage and keep the dishes in a sterile condition for a longer time.

At the beginning of this fiscal year, the replenishment of new glassware was placed under the Revolving Fund. Plans are underway for the conversion of the entire Glassware Unit operation to the Revolving Fund for FY 1969.

Serial No. DRS-LAB-1
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: CHRONIC MURINE PNEUMONIA OF THE ALBINO RAT

Previous Serial Number: SAME

Principal Investigator: James R. Ganaway

Other Investigators: Anton M. Allen
Thomas D. Moore

Cooperating Units: Rodent and Rabbit Production Section

Man Years

Total:	2.5
Professional:	.5
Other:	2.0

Project Description:

Objective: To elucidate the causation of Chronic Murine Pneumonia. To characterize the syndrome as it occurs in the NIH colonies. To recommend measures for the prevention and control under colony conditions.

Methods Employed: Microbiology, immunology, and pathology.

Major Findings: We have confirmed a previously published report concerning the prophylactic value of sulfonamides in preventing the development of Chronic Murine Pneumonia, thus indicating the importance of bacteria in the pathogenesis of this disease complex. Correspondingly, an association has been revealed between the severity of the lesions, as determined by histopathological studies, and the ease of isolation of a variety of bacteria from diseased rats. A manuscript covering the first phase of this work has been prepared and submitted for publication.

Significance: CMP is the greatest cause of morbidity and eventual mortality in rat colonies raised under conventional conditions. It particularly complicates, and may negate, results of any long-term study using the rat.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-LAB-2
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: FOCAL NECROSIS OF THE LIVER OF RABBITS

Previous Serial Number: SAME

Principal Investigator: James R. Ganaway

Other Investigators: Thomas D. Moore
Anton M. Allen

Cooperating Units: Rodent and Rabbit Production Section

Man Years

Total:	1.5
Professional:	.2
Others:	1.3

Project Description:

Objective: To characterize and identify the etiologic agent. To study the pathogenesis of the disease through experimental transmission studies. To recommend measures for control or prevention in the rabbit colonies.

Major Findings: The numbers of rabbits dying from this and other diseases has steadily declined during the past year. The reasons for this are not known. A serologic test has been developed which appears promising in preliminary studies. Further success would enable us to detect the presence of infection in the rabbit colony before spread of the disease and losses become great. Additionally, it should be possible to determine the relationship of our isolates from rabbits to that which causes Tyzzer's disease in mice.

Significance: This disease, occurring in epizootic proportions, has been the major cause of losses in the NIH rabbit production colonies in the past few years. The relationship of agents isolated from diseased rabbits at NIH to that causing Tyzzer's disease in mice remains unknown. A similar disease has also been recognized in subhuman primates by workers in England.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-LAB-3
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: FEBRILE HEMORRHAGIC DISEASE OF MONKEYS

Previous Serial Number: DRS-LAB-5

Principal Investigator: Anton M. Allen

Other Investigators: Nicola Tauraso, DBS

Cooperating Units: Laboratory of Virology and Rickettsiology, DBS

Man Years

Total:	1.0
Professional:	.3
Others:	.7

Project Description:

Objective: To study the pathogenesis of the disease.

Methods Employed: Pathology and microbiology methods were employed.

Major Findings: The clinical features and lesions of this highly fatal disease of monkeys were described in the 1965 Annual Report. Continued histopathology studies have borne out the original findings of hemorrhage in many tissues, systemic vascular stasis, glomerulo-nephrosis and widespread necrosis of lymphatic tissues. Similar lesions are being found in monkeys given the disease experimentally (transmission studies now being accomplished in closed quarters by the Laboratory of Virology and Rickettsiology, DBS). All evidence to date indicates that the disease is caused by a small virus with characteristics similar to those of arboviruses. No evidence has been found to implicate vector transmission, however. The disease has not occurred in man and has not been successfully transmitted to animals other than the monkey. Infected tissues derived from major outbreaks of similar disease in monkeys at Sukhumi Institute, USSR, and National Center for Primate Biology, Davis, California, are presently under study. Also, a search for susceptible hosts other than the monkey is being extended in order to increase knowledge of the possible danger of epizootics in resident mammalian populations in the United States.

Significance: The disease has not been reported in the literature. The causative agent has not been identified and, therefore, the health hazard to man is unknown. The disease may be introduced into the NIH primate colony again in the future.

Proposed Course: Continuation of pathology studies in conjunction with transmission and virus isolation studies by DBS. Manuscripts on the disease outbreak, pathology findings, and isolation of the causative agent have been submitted for publication.

Honors and Awards: None

Publications: A manuscript, "Symian Hemorraghic Fever. Part I. Clinical and Epizootiological Aspects of an Outbreak Among Quarantined Monkeys." and "Part II. Studies in Pathology," have been accepted for publication in The American Journal of Tropical Medicine and Hygiene.

Serial No. DRS-LAB-4
1. Laboratory Aids Branch
2. Animal Biologics Section
3. Poolesville

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: CANINE BLOOD DONORS

Previous Serial Number: NONE

Principal Investigator: Stephen Potkay

Other Investigators: R. D. Zinn

Cooperating Units: Experimental Surgery Section

Man Years

Total:	.55
Professional:	.05
Others:	.50

Project Description:

Objectives: To establish a colony of normal dogs to serve as blood donors. To determine the maximum frequency that a standard quantity of normal whole blood could be collected and to ascertain the required size for the donors.

Methods Employed: Five matched groups of laboratory reared dogs of the foxhound type were used. One unit of blood was obtained from each dog as follows: Group 1, once weekly; Group 2, once every second week; Group 3, once every third week; and Group 4, once every fourth week. Group 5 served as a control. The duration of the study was one year. Weekly blood samples were obtained from each dog to determine hematocrit, hemoglobin, total red and white blood cell counts, and reticulocyte count.

Major Findings: Dogs weighing 27 kg. or more were consistently able to donate normal blood at the rate of one unit every three weeks for a period of one year. Hematocrit and hemoglobin values of blood samples obtained from normal control dogs were significantly higher in winter than in summer. These differences appear to be associated with seasonal variations in temperature and sunlight.

Significance: The results indicate that a colony of donor dogs bled on a repetitive schedule can provide normal whole blood for research purposes. The use of such colonies to supplant the current practice of exsanguinating dogs for blood is proposed.

Proposed Course: Completed

Honors and Awards: None

Publications: A manuscript has been submitted for publication.

Serial No. DRS-LAB-5
1. Laboratory Aids Branch
2. Animal Biologics Section
3. Poolesville

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: THE EFFECTS OF A HEMATINIC ON THE BLOOD PICTURE OF DONOR DOGS

Previous Serial Number: NONE

Principal Investigator: Chester W. Anderson

Other Investigators: Stephen Potkay

Cooperating Units: None

Man Years

Total:	.40
Professional:	.20
Others:	.20

Project Description:

Objective: To determine the effects of an iron-rich hematinic on the erythroid cell series of canine blood donors, with a view toward increasing the blood production from the donor colony.

Methods Employed: Canine blood donors are bled at 2, 3, and 4 week intervals. They receive injections of iron-dextran which are designed to replace the iron loss accompanying volume blood donation. Injections are administered two days following the donation. Hematocrit, hemoglobin, red and white cell counts, and plasma protein determinations are made each week. The results are charted and compared to those obtained from control dogs which are bled on an identical schedule but do not receive iron injections.

Major Findings: Preliminary evaluation of the data indicates that parenteral supplementation with iron enhances red blood cell production in donor dogs, and decreases the time required for cellular elements to return to normal.

Significance: The current bleeding schedule for donor dogs is once every three weeks. Parenteral administration of iron to donor dogs may permit more frequent bleeding and result in better utilization of the donor colony.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-LAB-6
1. Laboratory Aids Branch
2. Animal Biologics Section
3. Poolesville

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: CANINE HEMOLYTIC ANEMIA

Previous Serial Number: NONE

Principal Investigator: Chester W. Anderson

Other Investigators: Mary C. Strott
Stephen Potkay

Cooperating Unit: None

Man Years:

Total:	.5
Professional:	.3
Others:	.2

Project Description:

Objectives: To add further to the knowledge of the following: 1) hemolytic anemia in the puppy caused by mating dogs and bitches with incompatible blood groups; 2) the mechanism of antibody transfer from the bitch to the pup; 3) the genetics involved in the transfer of the A factor in the canine.

Methods Employed: Matings between dogs of similar and incompatible blood groups are made. Bitches are titered throughout gestation to note any rise in titer of the anti-A factor. Puppies are blood grouped and titered for the anti-A factor before and after nursing for the first time, and daily for the first several days of life. Milk samples are titered for the anti-A antibody. Several matings of both a compatible and incompatible nature will be made with each bitch.

Major Findings: No results have been obtained yet.

Significance: This project will contribute to understanding mechanisms of disease which produce hemolytic anemia in puppies. This disease has not been clearly characterized in the literature but is generally included with other neonatal diseases under the heading of the fading puppy syndrome.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-LAB-7
1. Laboratory Aids Branch
2. Animal Biologics Section
3. Poolesville

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: HEMATOLOGIC AND BACTERIOLOGIC CHARACTERISTICS OF STORED CANINE BLOOD

Previous Serial Number: NONE

Principal Investigator: Stephen Potkay

Other Investigators: Chester W. Anderson

Cooperating Units: None

Man Years

Total:	.3
Professional:	.08
Others:	.22

Project Description:

Objectives: 1. To determine the bacteriologic status of blood derived from dogs that are normal and healthy as judged by applicable standard clinical and laboratory criteria, and to evaluate methods of obtaining sterile blood. 2. To determine the influence of anticoagulants, storage time, storage temperatures, and storage containers on whole canine blood. 3. To establish standards and methods for the routine sterility testing of blood produced by the Carnivore Unit.

Methods Employed: Blood (500 ml) was collected into blood bags using a hemolator or into vacuum bottles containing heparin, ACD, or CPD as anticoagulants. Blood was stored for 24 and 48 hours in heparin and for 3, 5, 10, and 21 days in ACD and CPD at 3° C. Determinations of the cellular components of the blood and its sterility were made at the end of these periods and compared to values obtained from the donor dogs immediately prior to volume collection.

Major Findings: Preliminary examination of the data indicates that bacterial contamination occurred in less than 5 percent of the samples. Cellular changes in refrigerated canine blood appear to be minor at 24 hours in the case of heparinized blood and at five days in the case of blood stored in ACD and CPD.

Significance: The feasibility of supplying sterile blood from a canine donor colony for use in research was demonstrated. Storage of heparinized blood for 24 hours and ACD or CPD blood for up to five days did not appear to reduce its usefulness for research purposes. Such blood can be issued in place of fresh blood, thus increasing the efficiency of the blood program.

Proposed Course: Completion

Honors and Awards: None

Publications: None

Serial No. DRS-LAB-8
1. Laboratory Aids Branch
2. Animal Biologics Section
3. Poolesville

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: FEED CONSUMPTION STUDIES IN THE CANINE

Previous Serial Number: NONE

Principal Investigator: Chester W. Anderson

Other Investigators: Stephen Potkay

Cooperating Units: None

Man Years

Total:	.8
Professional:	.2
Others:	.6

Project Description:

Objectives: 1. To determine the feed consumption per kilogram body weight in puppies from birth to one year of age. 2. To determine the feed consumption per kilogram body weight in bitches from breeding through parturition and lactation to weaning. 3. To determine the feed consumption per kilogram body weight in donor dogs on an active donation schedule. 4. To determine the feed consumption per kilogram body weight in "resting" dogs, such as open bitches, males, and cell donors.

Methods Employed: Dogs are weighed at weekly intervals and a record kept on the amount of feed consumed. The results are graphed, and values are determined.

Major Findings: Data have not been tabulated.

Significance: Standard growth curves will be obtained for American and English foxhounds where none presently exist. The data will also contribute to the determination of costs for housing and rearing dogs in the colony.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1967, through June 30, 1968

ENVIRONMENTAL SERVICES BRANCH Edwin M. Lamphere, Chief

I. SUMMARY

In order to increase the effectiveness of the Branch, an extensive reorganization was completed. The previous organization established on the basis of professional categories was abandoned in favor of the new organization, based on functional programs.

Much of the Branch workload continued to consist of solving individual problems on a short-term basis but this type of work has been declining for several years. More time is being spent on activities which lead to solving problems on a larger scale.

The development of complex environmental equipment has provided a better environment. Laminar flow hoods provide excellent protection for the research experiment but about 90 percent have been found to be less than fully satisfactory as delivered. A program of checking all newly purchased units was initiated.

Properly functioning chemical fume hoods can probably prevent more industrial hygiene problems in the laboratories than any other single factor. A survey of the approximately 800 hoods at NIH was completed. Each hood was marked with the condition under which it would operate satisfactorily.

An environmental survey of Buildings 29 and 29A was completed. In general, these surveys include determination of the work in progress, and a check of equipment, services, etc., used for control of any potentially hazardous material. A study carried out by the Branch has shown that the usual 30-minute autoclave cycle at 15 psi does not result in reliable sterilization of used glassware. Sixty minutes was found to be adequate.

Ultraviolet lamps are widely used at NIH to control microbiological contamination. Decontaminating capabilities disappear long before there is any visible evidence of bulb failure, however. A continuing program for checking all UV installation was initiated. The number of defective lamps ranged from a low of 15 percent to a high of 50 percent in various buildings.

An essential part of the biological hazards control activities is the development of facilities which will allow hazardous work to be carried out in an ordinary laboratory building. Such a facility was developed for

NINDB on the fifth floor of Building 36. All facilities necessary for working with hazardous organisms will be included.

Pseudomonas causes more hospital-acquired infections than any organism except Staph. aureus. A typing method was perfected and put into use which shows that the same types are found in the patient as in the environment. This has not been shown conclusively elsewhere.

Training is always important and is especially important in areas where competent personnel are in short supply. Hospital sanitarians are in very short supply, and a training program was developed and put into effect in conjunction with Bureau of Health Services.

II. BRANCH PROGRAMS

A. Objective

The objective of the Environmental Services Branch is to insure that a satisfactory environment is maintained at NIH and its field stations.

B. Current Programs

Attainment of the Branch objective was approached through four closely coordinated functional program areas:

1. Hospital Sanitation
2. Control of Biological Hazards
3. Industrial Hygiene
4. Water Supply

Administratively, the Branch continued to approach its objective by serving as a consultant to line management in the Institutes and Divisions. However, more emphasis was placed on working with individual scientists than in the past, since it is important to establish a base of mutual understanding, especially in the area of biological hazards control. Recognizing that scientists and I/D management have a wide variety of problems other than those associated with the environment, it is the policy of the Branch to present solutions in addition to a statement of the problems which are found. Every attempt is made to tailor these solutions to the administrative as well as the technical aspects of the problem.

Much of the Branch workload continued to be of a trouble-shooting nature, whereby an individual problem is solved in response to a specific request. This type of work has declined every year for the past several years, and more time has been spent on scheduled surveillance activities, special surveys, and solving problems on a much larger scale.

With regard to individual programs, hospital sanitation activities in the past have been concerned only with the patient care areas of Building 10, and have dealt with the environmental aspects of Clinical Center's overall infection control effort. During the past year, however, assistance was provided to NCI's clinical care program at the USPHS Hospital in Baltimore.

In the Clinical Center, all operating rooms are surveyed on a quarterly basis. Regular monthly surveys are carried out on the six Nursing Units where potential for cross-infection is greatest and on other randomly selected Nursing Units. Regular surveys are also carried out in any area where a potential problem of a temporary nature exists. The Formula Room, Central Sterile Supply, Physical Therapy, Blood Bank, Laundry, and similar areas are checked routinely. Samples of milk and formula room products are tested for bacterial contamination on a weekly or monthly schedule depending upon the item. As part of the hospital program, bacteriology laboratory services and professional consultations are furnished for any Clinical Center program which may involve environmental bacteriology. All laboratory work associated with insuring the necessary quality of air, food, and liquids on the Life Island project is carried out by the Branch.

A considerable amount of laboratory time is also furnished to the Department of Environmental Sanitation Control on studies of relative merits of various cleaning procedures, etc. In addition to the more routine work, the hospital program also carries out special studies for the purpose of solving problems before they occur and for upgrading the quality of the environment generally.

The program for control of biological hazards covers all NIH facilities, both at Bethesda and in the field, with the exception of the patient care areas of the Clinical Center. Activities of the biological hazards control program deal with identification and surveillance of potentially hazardous laboratory and animal room areas; regular surveillance of all animal facilities as part of an overall DRS effort; semiannual inspection of cafeterias, snack bars, and vending machine operations; general surveillance of housekeeping and waste disposal practices; developing, adapting, and evaluating equipment for containing hazardous organisms with minimum interference for the scientist; and development of containment systems and procedures which will allow hazardous work to be carried out in ordinary laboratory buildings.

The industrial hygiene program is similar in many ways to the biological control program except that it deals with potentially harmful non-living, rather than living, contaminants. Of greatest importance are toxic fumes generated in chemistry laboratories; some of the industrial processes carried out in DRS; and potentially harmful particulates, such as some of the carcinogenic chemicals. Other aspects of the industrial hygiene program deal with environmental factors which, while not harmful, affect the comfort, and therefore the efficiency, of NIH employees. Examples of items which are included in this category are noxious fumes, temperature extremes, odors, air pollution, and illumination.

Water supply activities are concerned primarily with the quality of potable and distilled water. Almost all present work is associated with monitoring water supplies and determining the cause of any deterioration in quality. All central distilled water supplies are checked weekly for specific resistance, with the exception of Building 10 where the supply is checked daily. An analysis of the copper content of all distilled water supplies at Bethesda and in the field is carried out quarterly. Potable water supplied to NIH is checked monthly for possible bacterial contamination and for adequate chlorine residual.

C. Program Progress and Accomplishments

While the amount of short-term work items of the trouble-shooting nature increased, at the same time the effort committed to problem solving and problem prevention on a larger scale also increased.

One of the most effective methods for preventing problems in laboratory buildings is to prevent these problems from being built-in during design and construction. The Branch has always devoted considerable time to review of plans for new facilities. In addition, to minimize future problems in the highly complex Building 41, an engineer was assigned on a half-time basis to watch for developing environmental problems and to serve in a liaison capacity between the NCI scientific staff and DRS construction engineers. The facilities to be constructed in North Carolina for the Division of Environmental Health Sciences are also very complex from the standpoint of controlling the research environment, and about 15 percent of an engineer's time has been devoted to this facility. The number of problems resolved during the construction of Building 41 has already shown that the effort expended in that direction is worthwhile. It is expected that the effort expended on the North Carolina activities will be equally worthwhile.

Development of more complicated methods and equipment for controlling the environment leads to a definite improvement in the environment, but not necessarily to a reduction in workload for environmental control personnel. As these methods and equipment become more complex, a greater amount of effort must be expended in insuring satisfactory operation. The problems associated with insuring satisfactory operation of laminar flow hoods are an example of this situation. These units, when operating correctly, provide protection to the research experiment which is not attainable by any other means. When not operating correctly, their usefullness is very limited. Satisfactory or non-satisfactory operation is almost entirely a function of filter installation. A program was initiated for acceptance tests of filters on all new units by the dioctyl phthalate method. Ninety percent of the newly purchased hoods were found to have defective filtering systems. A program was also initiated for checking the units after the filters have been changed.

Air filters, in addition to solving many problems associated with protecting the research experiment, also have widespread use in protecting personnel from potentially hazardous microorganisms. A program was initiated for checking exhaust filters on buildings such as 29A and Building 6, and the more critical biological safety cabinets. This program consists of a visual inspection every six months for physical damage, a rough efficiency check annually, and a careful check every two years, or when the filter is changed.

Properly functioning chemical and radiological fume hoods can probably prevent more industrial hygiene problems associated with the laboratory environment than any other single factor. In situations where the hood may not be adequate for hazardous work, it is important that the scientist be aware of the limitation. An initial survey of the approximately 800 fume hoods in Bethesda and at the Gerontology Building was completed. All hoods were marked with a label stating either the condition under which it will operate satisfactorily or that the hood is not satisfactory for use with hazardous materials. About 50 percent of the hoods in Building 10 and about 75 percent of the hoods in the other buildings met minimum standards for satisfactory operation.

With the performance of these hoods known, the next logical step in solving or preventing problems is to evaluate other aspects of the control of the more important potentially hazardous chemicals. Along these lines, work was initiated on the control of problems associated with the use of carcinogenic chemicals.

The use of ultraviolet lights is an important method for controlling microbiological contamination in research laboratories. Effectiveness, however, is dependent on proper maintenance. The fact that the bulb may emit visible light does not necessarily indicate any decontaminating capabilities. The bulk of the approximately 400 UV lamps in use at NIH are located in Buildings 7, 10, 29, and 29A. A surveillance program was initiated and all 280 lamps in Buildings 7, 29, and 29A, and about half of those in Building 10 were checked. The number of ineffective lamps was found to range from a low of 15 percent to a high of 50 percent in the various buildings. The UV installations will be checked at six-month intervals until a definite improvement is noted.

A necessary part of the biological hazards control program as conducted at NIH is the development of laboratory facilities which will allow hazardous work to be carried out in an ordinary laboratory building. Such a facility was developed for NINDB on the fifth floor of Building 36. This facility, which comprises the "C" corridor area, will be equipped with air locks, showers, pass-through autoclaves, special ventilation system, liquid waste treatment, and other appurtenances necessary to protect the scientists and the community.

Building surveys are another important aspect of the biohazards program and detailed surveys of Building 29 and 29A were completed. In brief, surveys of this type included determining the type of work in progress, and checking items such as (a) direction of air flow in critical areas, (b) autoclaves, (c) UV lights, (d) waste handling practices, (e) containment equipment, and (f) housekeeping practices.

Work is now underway at the Middle America Research Unit on implementing the ESB recommendations for critical immediate needs for controlling biological hazards. This work is fairly extensive and includes filtration of air from the hot suite, installation of a large pass-through autoclave and a cage washer, and modification of housekeeping practices.

While considerable attention is given to checking autoclaves for satisfactory mechanical operation, procedures which are tailored to fit the material to be decontaminated are also very important. A study carried out by the Branch has shown that the usual 30-minute sterilizing cycle at 15 psi is not adequate when using the standard NIH autoclave pan. A 45-minute cycle will result in survival of indicating organisms in up to 10 percent of the cases. A 60-minute cycle has been shown to be adequate, however, and the Institutes have been advised of these findings.

General cleanliness is an important step in control of undesirable microorganisms, both in the laboratory and in the hospital. At present, a real problem results from casework which is difficult to clean. ESB has a representative on the National Sanitation Foundation's "Committee on Hospital Cabinetry and Laboratory Furniture." This committee was organized to develop standards for construction which, among other things, will insure easy cleanability. It is expected that the standards will be completed by the fall of 1969.

During the past year a DRS program for supporting the Institutes in the animal care field was established. The DRS team consists of staff members from LAB and ESB. In connection with this program, inspections for conformance with accreditation standards of the American Association of Laboratory Animal Care were carried out in NCI, NIDR, and NIAID. ESB was responsible for evaluation of sanitation and physical facilities. In general, these aspects were reasonably satisfactory.

Pseudomonas is a very common organism in hospitals and will grow almost anywhere that there is a little moisture. In the Clinical Center, Pseudomonas infections are more common than those caused by any organism except Staph. aureus. A typing method was adapted in essential features in FY 1967 and was perfected and put into use in 1968. It has been possible to show that the same types are found in the infected patient and in the environment. This has not been shown conclusively elsewhere and it gives the justification necessary for a greater emphasis on decontaminating the sources of the organism.

Training is always important in the environmental health field and particularly important in areas where competent personnel are in short supply. Qualified hospital sanitarians are needed by the Service and other health-oriented organizations, but are very rare. A cooperative Bureau of Health Services-NIH training program for hospital sanitarians was developed and put into effect in January 1968.

In order to increase the effectiveness of the Branch, an extensive reorganization was carried out. Previously, there have been two sections--one oriented toward the physical sciences and the other oriented toward the biological sciences. This type of organization results in good technical supervision but does not easily lend itself to programs which require both types of personnel on a day-to-day basis. Therefore, an organization based on functional programs rather than professional disciplines was adapted. The reorganization also provided the means to take better advantage of opportunities for program progress in the areas of research and development; training; and organized liaison with design, construction, and maintenance groups.

The detergent formulation used at NIH through FY 1968 was developed in 1954. Characteristics of the water supplied to NIH have changed drastically since that time, and the old formula is no longer compatible with present water quality. In addition, there has been considerable progress in detergent chemistry in the past 14 years. A consultant was retained to investigate NIH's washing needs and to develop formulas for cage washing and for glassware washing.

D. Problems

There were a variety of internal problems resulting from the fact that the organizational structure did not mesh with program needs and the fact that there were not sufficient senior staff members to provide continuous guidance to the large number of new junior personnel. All non-supervisory engineers, and most of the non-supervisory professionals in other categories transferred and were replaced during the last six months of calendar 1966. There is no way to avoid the biannual turnover for engineers as long as primary reliance is placed on young officers on two-year career development assignments. This problem will be alleviated by staffing partially with the higher-grade engineers which the present program requires. It is expected that problems attributable to an inconvenient organizational structure will be solved by the reorganization.

While there was marked progress in the area of biohazards control, it was sufficiently slow to leave many unresolved problems, and to cause much staff frustration.

In the situations where the scientist resists using containment equipment or other protective devices, very often one of two things occurs: (1) there is agreement that action should be taken but nothing is done, or (2) questions are raised as to whether ESB has correctly assessed the risk. The solution to the question of risk assessment will also tend to alleviate the remainder of problems. It is planned to request the Institutes to appoint a committee of at least three scientists who will assess the risks in their Institute. Under this situation ESB would continue to locate problems and to carry out detailed investigations. The committee would decide the degree of hazard involved, and ESB would recommend protective measures commensurate with the hazard. The virologist available on the ESB staff will also be of considerable assistance in problems of this type.

Lack of knowledge of even near-term Institute plans was more of the problem than usual this year. For example, many potentially hazardous laboratory operations will move to Building 37 when it is completed and, while some steps are underway, the necessary facilities are not being provided. As of May 1, space allocations were not sufficiently definite to allow for provision of the necessary protective measures. In many cases little can be done about lack of knowledge of Institute plans. However, when the problem involves facilities, it may be possible to delay design and construction until adequate plans are submitted. This approach will be pursued with the Director's Office, DRS.

A variety of problems arose during the year with other organizational groups involved in environmental health activities. Problems of this type will probably always exist but will be lessened if mutual agreement on respective roles can be reached. A series of discussions has been initiated for the purpose of reaching such an agreement.

E. Program Plans

No change in objectives of the Branch is foreseen, but some changes in staffing patterns and in methods of approach are planned. The heavy reliance on staffing with junior engineers and sanitarians will be lessened, since the Branch cannot function at an optimum degree of effectiveness if the non-supervisory staff leaves and must be replaced every two years. This change in staffing pattern is also in keeping with plans for a somewhat modified approach in dealing with the Institutes. While the Branch will continue to function in a consultant capacity to Institute management, more emphasis will be placed on working with and convincing the individual scientist. This requires personnel in whom the researcher can have confidence, and who can operate independently of detailed ESB supervision. With the relatively large number of non-clear-cut situations which occur, particularly in the biohazards control area, the practice of locating potential problems in the laboratories and submitting recommendation to the Scientific Director has not resulted in the desired progress.

It is planned that much more emphasis will be placed on training than in the past, with informal as well as formal training receiving attention. The informal training will be an integral part of the plan to work more closely with researchers. With regard to formal training, a training officer has been recruited to initiate, coordinate, and follow through on Branch activities in this area. It is planned to start training courses for animal caretakers in conjunction with LAB, and for laboratory technicians in connection with biological safety programs. In addition, it is planned to expand the training effort in the Clinical Center.

Development activities will receive more attention than in the past, and a definite Branch program in this area will be carried out. It is expected that development of laboratory and field methods for evaluating the environment, evaluation of laminar flow and similar equipment, and evaluation and control of the shedding of microorganisms from the skin will receive major emphasis.

Two new activities, within already developed program areas, will be started during the coming year. A virologist was recruited, and an active virology laboratory program will be carried out in support of the biological control activities. Initial emphasis will be placed on developing methods for collecting viruses from the environment. Another activity to receive priority this coming year is evaluation of problems associated with the use of carcinogenic chemicals in laboratories and the development of whatever control measures are indicated.

F. Publications

Cook, R. O.: A New Ventilated Isolation Cage, *Applied Microbiology*, May 1968.

Leary, A. G. and Radden, E. B.: Evaluate Performance of HEPA Filters in Clean Benches, *Heating, Piping-Air Conditioning,* 39:117-119, Sept. 1967.

Levitan, Seidler, Herman, L. G., and Strong: Bacteriological Surveillance of the Patient Isolator System, *Archives of Environmental Health*, Vol. 14, pp. 837, 1967.

Herman, L. G.: Control of Biological Agents as Contaminants in Microbiological Laboratories, *Disinfection, Sterilization and Preservation*, published by Lea & Febiger, Philadelphia, 1968, Pt V, Ch. 34, pp. 543, Editors: Lawrence, C. A. and Block, S. S.

Fox, D. G.: Contamination Levels in a Laminar Flow Operating Room, *HOSPITALS*, *Journal of the American Hospital Association,* June 1968.

Herman, L. G.: Decontamination and Sterilization, *Executive Housekeeper*, May 1968.

Herman, L. G. and Powell, W. V., Biological Agents as Contaminants in the Industrial Laboratory, *Developments in Industrial Microbiology*, Vol. 8.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1967, through June 30, 1968

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH Dr. Lester Goodman, Chief

I. SUMMARY

Fiscal year 1968 was a period of vigorous activity and substantive progress toward fulfilling Branch objectives. For the past several years, BEIB has been building a highly competent group of professional and technical personnel. The Branch has now gained a reputation as a national focal point for engineering competence and authority in biomedicine. Major emphasis is placed on stimulating direct collaboration between BEIB professional staff and intramural researchers in the conduct of biomedical research and development programs. In addition, individual improvement is promoted through an education and training program to further enhance the Branch's capabilities and effectiveness.

The Technical Services sections, Instrument Fabrication and Systems Maintenance, achieved unprecedented peaks in productivity during FY 1968. These sections performed 11,550 assignments during the year at a value of $1,026,000, an increase of 5 percent in jobs and 11.3 percent in dollars over the previous annual high, reached in FY 1967.

Branch professional staff have been involved in approximately 400 research and development tasks. Although the total number of projects has not changed significantly from the previous year, there has been a distinct increase in the level of sophistication of technical collaboration and support provided to the NIH community, with a concomitant increase in the percentage of long-term programs. The year has seen noteworthy original contributions in the areas of artificial organs, materials, laser technology, mechanization, automation, physiological monitoring, patient care, and physiological systems analysis.

The concept of satellite operation has been realized in substance. The Clinical Center Technical Support Unit has been reorganized, and one new satellite located in NCI, Building 37, is expected to be functioning early in FY 1969.

A modest program has been initiated for more economic use of scientific equipment. Experience to date shows growing acceptance of the concept by the NIH community.

Full realization of potential has been curtailed by budgetary restrictions. However, a firm base has been established for prompt, positive action when the occasion demands.

II. BRANCH PROGRAMS

A. Objectives

To fulfill the need for engineering knowledge and technical skills in pursuit of health research at NIH.

To provide direct and consultative engineering support to clinical and biomedical research projects, including advice on systems analysis, experimental design, and synthesis of technical expedients.

To design, develop, fabricate, and evaluate special-purpose devices and systems not commercially available.

To maintain and repair scientific laboratory and clinical equipment.

To provide communication between NIH and the general public on engineering support to clinical and biomedical research.

To serve as a source of informed authority in matters pertaining to engineering in medicine and biology.

B. Current Programs

The primary purpose of the Branch is to provide service and support to the intramural program of the NIH. BEIB activities, therefore, are identified with many of the individual programs that constitute the intramural research effort. The overall Branch program is best described as the coordinated effort of its operating units.

1. Instrument Fabrication Section

a. Prepares minor designs of, makes modifications to, and fabricates biomedical equipment and instrumentation systems.

b. Produces devices requiring special tools and skills in the electronic, electrical, glass, mechanical, optical, rubber, plastics, welding, and sheet metal categories.

2. Systems Maintenance Section

a. Maintains and repairs biomedical equipment and instrumentation systems.

b. Instructs technicians and scientists in the proper use and operation of especially complex instruments and devices.

3. Electrical and Electronic Engineering Section

a. Collaborates with intramural professional staff in fundamental and applied projects relevant to biomedical research and health care.

b. Provides consultative electrical and electronic engineering support to biomedical research projects at NIH.

c. Designs, develops, and evaluates electrical and electronic instrumentation and equipment used in research and clinical applications.

d. Provides communication between NIH and the general public on electrical and electronic engineering support to biomedical research and clinical practice.

4. Chemical Engineering Section

a. Provides consultative chemical engineering support to biomedical research projects at NIH.

b. Designs, develops, and evaluates chemical instrumentation and equipment used in research and clinical applications.

c. Provides communication between NIH and the general public on chemical engineering support to biomedical research and clinical practice.

5. Mechanical Engineering Section

a. Provides consultative mechanical engineering support to biomedical research projects at NIH.

b. Designs, develops, and evaluates mechanical instrumentation and equipment used in research and clinical applications.

c. Provides communication between NIH and the general public on mechanical engineering support to biomedical research and clinical practice.

6. Branch Engineers

These senior professionals serve as staff consultants in the Office of the Chief and are assigned to organize, conduct, and oversee particular comprehensive, long-range research and development projects. They provide unique scientific and engineering knowledge to the Branch and NIH.

7. Supply Unit

Provides for the acquisition and disposition of materials, parts, and equipment required for Branch operations. Maintains controlled inventory stocks and records.

8. Satellites

Satellites are technical support units, composed of selected engineers and technicians with appropriate shop facilities, located in certain areas where it is beneficial to make typical BEIB support and service immediately available via a controlled degree of decentralization. They are responsive to demands of local programs and operate as integral parts of the resident team but are administratively responsible to the central Branch. Each is especially tailored to meet specific needs of the host Institute or Division. Satellite operation supplies the host with the advantages of a proprietary technical group and maintains the chief benefits of centralized resources.

C. Program Progress and Accomplishments

The effectiveness of service and support by BEIB to the research program of NIH continues to improve. This results directly from (1) emphasis on the role of professional physical scientists and engineers as collaborators in health research, and (2) improved stability of the technical services work force at a higher level of experience and competence. The entire staff of BEIB shares this improved status with the direct results of greater personal pride in the Branch, improved morale, increased productivity, and higher efficiency.

1. Workload

Modifications in workload data gathering and reporting, initiated in the previous year, have been a significant aid in Branch management. Improved methods are evolving as experience increases and program activities progress.

The IFS processed approximately 4,180 different project assignments involving minor design, fabrication, or major modification. The SMS processed approximately 7,370 different project assignments involving maintenance, repair, or minor modification.

BEIB engineers were involved with approximately 400 different research and development tasks. The number of comprehensive long-range projects with which the Branch is involved has significantly increased as BEIB's role in the NIH program evolves. Individual projects of special research interest are detailed in Section III. Program areas that continue to receive considerable attention are as follows:

a. Improved techniques and systems for physiological monitoring in surgery and intensive patient care.

b. Systems design and construction for mechanizing and automating laboratory and clinical procedures.

c. Research and development in artificial organs and prostheses, including studies of basic phenomena and construction of devices for artificial heart components and hemodialysis therapy.

d. Systems design and construction of devices to gain more benefits from automatic data processing and electronic computation and control.

e. Improving tools for cardiac and neurosurgery.

f. Developing the laser as a useful device in life science research and therapy, as well as extending its physical potential.

g. Research and development on the synthesis of special materials for biomedical applications.

h. Analysis and modeling of physiological phenomena especially related to therapeutic processes.

2. Technical Advances

BEIB has delivered a considerable number of special-purpose devices and systems in support of Institute research projects. Items of more than casual interest follow:

A fixed bed adsorber device produces platelet-deficient animal blood more effectively than other known chemical or radiological techniques.

An electronic control for a pneumatic heart assist device appropriately operates a solenoid valve, based on ECG and blood pressure and provides several operating modes, parameter adjustments, and hazard prevention interlocks.

A very small mass photoelectric displacement transducer measures heart muscle motion with resolution to fractions of a micron.

A temperature monitoring system for hypothermia operations in neurosurgery furnishes 0.1°C accuracy and two data recording channels.

A programmable digital sample dispenser expedites operation of an automated clinical chemistry system.

A muscle motion transducing system, featuring very light mechanical loading of the muscle, provides voltage readouts for acceleration, velocity, and displacement.

An impedance, voltage, and current monitoring unit presents a visual display of electrical impedance, voltage, and current between any two selected probes in the patient's brain.

A feedback control system automates operation of a Langmuir trough surface tension apparatus.

A multiple auto-valving device for chromatographic cabinets permits initiation of solvent flow automatically at any preset time.

A device to produce intra-ventricular fibrillation for an extended period of time during surgery enables quick return to autonomous function following heart-lung bypass disconnect.

A photoelectric blood clot sensor aids in studying thrombogenic properties of prosthetic materials.

A servo control system maintains a preset stress level in heart muscle during a portion of each cardiac cycle.

An improved pipette plugging machine accepts mixed sizes of pipettes and plugs them at a rate of 25 per minute.

A solid state electronic differential calorimeter features automatic computation of the difference in specific heats.

A rat activity monitor senses activity photoelectrically and totalizes events separately for six compartments.

A media changer automatically deracks, uncaps, replaces spent media with fresh media, then recaps, and reracks test tubes at the rate of one every 12 seconds.

An electronic log-log converter converts exponentially decaying current from a photomultiplier to a linear ramp voltage and differentiates to obtain an output proportional to the rate constant.

A mass ratiometer improves accuracy and precision of mass spectrometer analyses.

A solid state log converter for use with an existing spectrophotometer, features digital readout and operation with currents down to 100 picoamperes.

An electronic monitor for the 10A Cardiac Surgery recording system provides an instant check of system readiness and indicates source of malfunction.

A ground loss alarm safety system for operating suites responds when patient electrical ground is interrupted.

A pyrex multichannel electrophoresis apparatus enables analyses of macromolecular mixtures using polyacrylamide gels which are effective over a maximum range of pH and pore sizes.

Vacuum formed plastic disposable toilet inserts to collect specimens significantly reduce costs for large-scale patient studies.

A molded plastic stereotaxic platform for use on monkeys replaces more expensive conventional all-metal devices.

A triple X-ray defraction detector provides for three simultaneous recording channels.

A new perfusion chamber improves studies of kidney tubule function.

An automatic dispensing and recycling viscometer expedites analyses of chemical reaction rates with superior resolution and speed.

A novel recycling device for a counter current distribution machine, used for the separation of antibiotics, reduces changeover time between modes of operation from 30 minutes to 3 seconds.

3. Inventory and Supply

Technical procurement operations, heretofore split between management and fee-for-service activities, have been centralized within the supply unit. The arrangement has improved service and provided Branch management with better cost analysis of operating expenses.

Inventory replenishment contracts with the Beckman Corporation, Spinco and Spid Divisions, were negotiated during the year and resulted in more efficient and timely acquisition and stocking of replacement parts.

The use of blanket purchase orders was expanded considerably during the past year. Simplified procurement procedures, resulting from increased delegation of procurement authority from the SMB Procurement Section, have materially reduced the volume of formal purchase orders and produced concomitant savings.

4. Service Contracts

The Branch encourages the use of contractual services, with special emphasis on service-type contract with certain scientific equipment suppliers. Fixed price contracts with Beckman Corporation, Spinco and Spid Divisions, have proven beneficial to the scientific staff. The class of equipment covered includes centrifuges, spectrophotometers, pH meters, gas chromatographs, and liquid scintillator counters. Specific benefits provide:

a. Consulting services on custom engineering modifications and special accessories.

b. Information for researchers and technicians on new techniques and applications as developed.

c. Guidance and assistance in setting up scheduled service and maintenance programs.

A contract with the Materials Evaluation Laboratory, National Bureau of Standards, provides NBS equipment and personnel for testing elastomer formulations and specimens provided by BEIB and reports on data such as rheograph curves and stress-strain relationships. It further provides data in support of the biomaterials development program which is not available at NIH because of lack of suitable equipment.

5. Training

An effective professional and technical training program provides improved, up-to-date support to NIH in engineering, fabrication, and maintenance. Forty-nine employees participated in academic and technical courses. Thirty-eight ($382\frac{1}{2}$ man days) attended formal education and training courses. Eleven (73 man days) received specialized training on scientific equipment at suppliers' plants and at the NIH.

One BEIB engineer has been on full-time assignment to pursue the MS degree at the University of West Virginia.

The following were conducted jointly by BEIB/SMS and Beckman Instrument Company under the terms of Contract #43-68-66:

a. A one-day "Spinco Amino Acid Analyzer" course presented by Dr. Erhard Gross, NIAMD, to 30 scientific and technical attendees.

b. A two-day seminar on "Zonal Centrifugation." The seminar, repeated six times, was attended by a total of 120 employees, primarily from the NIH and other Government agencies in the Washington Metropolitan area. The instructor was Dr. H. E. Bond, NCI.

c. A three-week laboratory session, part of the "Analytical Ultracentrifugation" course offered by the NIH Graduate Program, FAES, was attended by 26 students. Instructors were Dr. Samuel Luborsky, NCI, and Dr. Marc Lewis, NINDB.

d. A 30-week course on "Instrumentation Electricity," tailored to medical equipment for medical equipment repairers, met for 1½ hours per week. Ten SMS medical equipment repairers participated. Mr. Leonard Aberbach, SMS, was the instructor.

6. Equipment Utilization

In cooperation with the Supply Management Branch, BEIB has developed the mechanism for utilization of used scientific equipment. When items are declared excess to SMB, the property transfer orders are routed through BEIB, who inspect the equipment and judge the feasibility and cost of repair. When advisable, BEIB restores the equipment to good condition.

The SMS, BEIB, maintains a comprehensive inventory of useful scientific equipment which is made available for loan to NIH researchers on a request basis. When a request to use a device is for one year or more, a property transfer is arranged. When the request is for short-term use, it is loaned without cost and then returned to the loan pool.

BEIB also maintains a sizable number of certain classes of equipment to replace components when the user's equipment is in the shop for repairs.

At the present time, there are about 400 items in the loan pool. Approximately 100 of these are on loan at any given time. Over the course of the past year, approximately 100 items have been acquired from SMB's excess property, refurbished by BEIB, and transferred to users on a permanent basis.

7. Satellites

a. The Building 10 Maintenance Unit has been reorganized to improve coordination of technical services and support for Clinical Center programs. It has been renamed the Building 10 Satellite Unit and placed under control of the Assistant Chief for Technical Services, BEIB.

b. Approval has been obtained for establishment of a new satellite technical support unit for the National Cancer Institute in Building 37. Operations are expected to commence early in FY 1969.

D. Problems

1. Personnel

Increased Federal salaries, improved recruitment practices, and generally more progressive application of policies and procedures have enabled the Branch to improve its support to the NIH intramural research program. However, its potential is yet far from being realized.

Ceilings restrictions in effect throughout the fiscal year have drastically curtailed program developments in the important areas of artificial organs, materials development, and mechanization and automation of laboratory and clinical procedures. The restrictions, unfortunately, have been imposed at a time when the needs of these critical program areas require and can attract well qualified and highly motivated professional people.

The ready availability of superior Commissioned Corps engineers and scientists has been an enormous boon to BEIB professional development. Many of these, however, anticipate tours of duty no longer than two years. The need exists to emphasize recruitment of career civil servants at high professional levels to assure stability for the future.

2. Space

The acquisition of 5,600 square feet of new space in Building 13 in 1967 temporarily relieved a serious problem of overcrowding that is now recurring. The Systems Maintenance Section, to which the bulk of the new space was allocated, has experienced a 39 percent increase in Building 13 staff during 1968. There has been no increase in available space.

Had not drastic personnel ceiling restrictions been imposed during the year, overcrowding for the engineering sections would now be most serious. It is essential that appropriate measures be planned for the time when such constraints are relaxed.

It is expected that expansion of the equipment utilization program will soon require additional space adjacent to the Systems Maintenance Section.

Renovation of the Building 10 Satellite Unit space has relieved the problem of overcrowding in that area somewhat. Additional adjacent space is still required, however, if the satellite is to fulfill its purpose most effectively.

E. Program Plans

The Electrical and Electronics Engineering Section and the Mechanical Engineering Section have been brought to near "critical" size for the level of current operations. The Chemical Engineering Section has clearly demonstrated the innovations that the field it represents can introduce into health research. Unfortunately, severe personnel ceiling constraints have curbed its intended growth rate, and it remains far below "critical mass." Continued emphasis will be placed on improving the engineering sections in terms of numbers and professional competence, with special attention being given to Chemical Engineering.

Progress continues in the level of contribution by BEIB scientists and engineers to NIH research programs. The innovating and developing of new concepts and their acceptance by intramural scientists have grown consistently. The Branch expects to continue its efforts in promoting these trends and extending work in areas such as physiological monitoring for patient care, new diagnostic and surgical tools, mechanization and automation, artificial therapeutic devices, laser technology, physiological systems analysis, and biomaterials. Other major issues that may be encountered include:

1. Implementation of a new NIH organization for more comprehensive coordination of engineering and physical sciences with medicine and biology.

2. Installation and operation of an NIH-wide economic scientific equipment utilization program.

3. Establishment of additional satellite technical support units.

4. Improvement of mechanisms for development and transfer of engineering innovations to biomedical research applications within the NIH structure.

F. Publications, Presentations

1. Publications

Battig, C. G.: Checking for electrical shock hazards. Anesthesiology. (In press)

______: Electrosurgical burn injuries and their prevention. JAMA. (In press)

Bischoff, K. B. and Dedrick, R. L.: Pharmacokinetics of artificial kidney therapy for poisons. In Proceedings of the Annual Conference on Engineering in Medicine and Biology, 1967, Boston, Mass. The Conference Committee for the 20th Annual Conference on Engineering in Medicine and Biology. Murray Eden, Chairman, MIT, 1967, Vol. 9, p. 8.6. (Paper presented in Boston, Nov. 1967.)

______ and ______: Thiopental pharmacokinetics. Journal of Pharmaceutical Sciences. (In press)

______: Discussion of correlations of blood coagulation with surface properties of materials. Journal of Biomedical Materials Research. (In press)

Boretos, J. W. and Pierce, W. S.: Segmented polyurethane: a new elastomer for biomedical applications. Science 158:1481-1482, Dec. 16, 1967.

______: Procedures for the Fabrication of Segmented Polyurethane-polymers into Useful Biomedical Prostheses. Bethesda, Md., Bldg. 13, Rm. 3W13, NIH, 1968, 16pp.

Cohen, G. S.: A data acquisition system for psychophysiological research on newborns. In Proceedings of the Annual Conference on Engineering in

Medicine and Biology, 1967, Boston, Mass. The Conference Committee for the 20th Annual Conference on Engineering in Medicine and Biology. Murray Eden, Chairman, MIT, Vol. 9, p. 25.2. (Paper presented in Boston, Nov. 1967.)

______: Design of the operating room, In Segal, B. L. and Kilpatrick, D. G. (Eds.): Engineering in the Practice of Medicine. Baltimore, The Williams and Wilkins Co., 1967, pp. 75-82.

______: State of the art: intensive care equipment. Proceedings of 6th National ISA Biomedical Sciences Instrumentation Symposium. (In press) and Instrumentation Technology. (In press) (Paper presented in Pittsburgh, Pa., May 1968.)

Dedrick, R. L., Bischoff, K. B., and Leonard, E. F. (Eds.): The artificial kidney. Chemical Engineering Progress Symposium Series, No. 84, New York, American Institute of Chemical Engineers, 1968, Vol. 64, 123 pp.

______ and ______: Pharmacokinetics in applications of the artificial kidney. Ibid. pp. 32-44. (Paper presented at meeting of AICHE, Tampa, Fla., May 1968, by Dr. Dedrick.)

______: Observations on biomedical engineering. Transactions of the New York Academy of Sciences. (In press) (Paper presented in New York, Feb. 1968.)

Feigl, E. O., Simon, G. A., and Fry, D. L.: Auxotonic and isometric cardiac force transducers. Journal of Applied Physiology 23: 597-600, Oct. 1967.

Friauf, W. S.: Novel applications of feedback in biomedical instrumentation. In Proceedings of the Annual Conference on Engineering in Medicine and Biology, 1967, Boston, Mass. The Conference Committee for the 20th Annual Conference on Engineering in Medicine and Biology. Murray Eden, Chairman, MIT, 1967, Vol. 9, p. 35.1. (Paper presented in Boston, Nov. 1967.)

Gombos, E. A., Metz, H., and Chalifoux, H.: Development and organization of a large haemodialysis centre. In Kerr, D.N.S. (Ed.): Replacement of Renal Function. Proceedings of the Third Conference of the European Dialysis and Transplant Association, Lyons, France, June 1966. New York, Excerpta Medica Foundation, International Congress Series No. 131, 1967, pp. 117-121.

Goodman, L.: Biomedical engineering brings technical applications to problem solving in medical research, treatment. American Engineer, 18-19, Feb. 1968.

______: Medical control systems. In revised edition, McGraw-Hill Encyclopedia of Science and Technology. (In press)

______: Clinical implications of equipment characteristics. Proceedings of Meeting, Computer Applications in Clinical Electrocardiography, American College of Cardiology. (In press) (Paper presented at Washington, D. C., Nov. 1967.)

______ and DeBroske, J. M. F.: The Shop. BIAC Information Module M17. Washington, D. C., BioInstrumentation Advisory Council, 1968, 8pp.

Hoye, R. C., Gart, J., Weiss, G. H., Riggle, G. C., and Ketcham, A. S.: Potential of laser oncolysis with pretreatment x-irradiation. Radiation Research 32: (No. 1) pp. 112-116, Sept. 1967.

______, Riggle, G. C., and Ketcham, A. L.: Laser destruction of experimental tumor state of the art and protection of personnel. American Industrial Hygiene Association Journal 29: (No. 2) pp. 173-180, March-April 1968.

Ketcham, A. S., Hoye, R. C., and Riggle, G. C.: A surgeon's appraisal of the laser. Surgical Clinics of North America 47: (No. 5) 1249-1263, Oct. 1967.

Kolobow, T. and Dedrick, R. L.: Dialysate capacity augmentation at ultra-low flow rates with activated carbon slurry. In Schreiner, G. E. (Ed.): Transactions of the American Society for Artificial Internal Organs, Atlantic City, N. J., April 1966. Dr. G. E. Schreiner, Dept. of Medicine, Georgetown University Hospital, Washington, D. C. 1966, Vol. XII, pp. 1-6.

______ and ______: Dialysate capacity augmentation with activated carbon slurry. In Kerr, D.N.S. (Ed.): Replacement of Renal Function. Proceedings of the Third Conference of the European Dialysis and Transplant Association, Lyons, France, June 1966. New York, Excerpta Medica Foundation, International Congress Series No. 131, 1967, pp. 375-377.

Leonard, E. F. and Dedrick, R. L.: The artificial kidney: problems and approaches for the chemical engineer. In Dedrick, R. L., Bischoff, K. B., and Leonard, E. F. (Eds.): The artificial kidney. Chemical Engineering Progress Symposium Series No. 84, New York, American Institute of Chemical Engineers, 1968, Vol. 64, pp. 15-31.

Norris, G. F., Banfield, W. G., and Chalifoux, H. D.: Tissue processor for automatic dehydration and infiltration of small specimens. Science Tools 14: 13-14, Apr. 1967.

Peterson, J. I.: Urinary glucose measurement. Clinical Chemistry (In press) (Paper presented at Symposium on Low Molecular Weight Urinary Constituents, Oak Ridge National Laboratory, Oak Ridge, Tenn., Dec. 1, 1967.)

______: Gel electrophoresis destaining apparatus. Analytical Biochemistry (In press)

______ and Young, D. S.: Evaluation of the hexokinase-glucose-6-phosphate dehydrogenase method of determination of glucose in urine. Analytical Biochemistry. (In press)

Pierce, W. S., Turner, Jr., M. C., Boretos, J. W., Metz, H. D., Nolan, S. P., and Morrow, A. G.: Mechanical left ventricular assistance: experimental studies using an implantable roller pump. In Schreiner, G. E. (Ed.): Transactions of the American Society for Artificial Internal Organs, Chicago, Ill. April 1967. Dr. G. E. Schreiner, Dept. of Medicine, Georgetown University Hospital, Washington, D. C., 1967, Vol. XIII, pp. 299-305.

Riggle, G. C., Hoye, R. C., Ketcham, A. S., and Hawkins, R. W.: Development of a high energy neodymium laser system for surgical use. In Jacobson, B. (Ed.): Digest of the Seventh International Conference on Medical and Biological Engineering, Stockholm, Aug. 1967. The Organizing Committee for the International Conference on Medical and Biological Engineering, Sven Brohult, Conference Chairman, The Royal Academy of Engineering Sciences, Stockholm, 1967, p. 164. (Paper presented by Mr. Riggle in Stockholm, Aug. 1967.)

Turner, M. C., Pierce, W. S., Fogle, J. L., and Boretos, J. W.: An implantable heart assist pump system. Ibid. p. 386. (Paper presented by Mr. Riggle in Stockholm, Aug. 1967.)

2. Presentations

Battig, C. G.: Burn hazards associated with the electrosurgical unit. Workshop for Electrical Hazards in Hospitals, National Academy of Sciences, Washington, D. C., April 1968.

Bischoff, K. B.: The chemical engineering kinetics laboratory. American Society for Engineering Education at Michigan State University, Michigan State University, East Lansing, Mich., June 1967.

Dedrick, R. L.: Kinetics of activated carbon kidney. American Society for Artificial Internal Organs. Chicago, Ill., April 1967.

_______: Biomedical engineering at NIH. Bioengineering Seminar, University of Maryland, College Park, Md., Oct. 1967.

_______: Biomedical engineering membership activities in the American Institute of Chemical Engineers. 20th Annual Conference on Engineering in Medicine and Biology, Boston, Mass., Nov. 1967.

_______: Biomedical engineering at NIH. Biomedical Engineering Seminar of Johns Hopkins University, Baltimore, Md., Dec. 1967.

_______: The structure and activities of BEIB. PHS Orientation Course for Engineers and Related Environmental Personnel, Cincinnati, Ohio, Jan. 1968.

_______: Artificial organs. Conference on "Science and Engineering of the Living System," Drexel Institute of Technology, Philadelphia, Pa., March 1968.

_______: The artificial kidney. Chemical Engineering Seminar of Princeton University, Princeton, N. J. , April 1968.

Dedrick, R. L.: Engineering in medicine. Lecture - Engineering Faculty and Graduate Students, Oklahoma State University, Stillwater, Oklahoma, May 1968.

Goodman, L.: As NIH Project Officer, spoke on the objectives and needs of NIH as related to the interplay of engineering with biology and medicine at the first meeting of the NAS-NAE Study Group on Interplay of Engineering with Biology and Medicine, held at the National Academy of Engineering, Washington, D. C., Oct. 1967.

______: Biomedical engineering activities of the American Society of Mechanical Engineers. 20th Annual Conference on Engineering in Medicine and Biology, Boston, Mass., Nov. 1967.

______: Technology-medicine-information. Biological Sciences Section, Washington Chapter of the Special Librarians Association, Washington, D. C., Nov. 1967.

______: Engineering developments for biology and medicine. DHEW Press Conference, Washington, D. C., Dec. 1967.

______: Engineering in medicine and biology. The Fred Gale Show, Radio Station WWDC, Washington, D. C., Jan. 1968.

______: Engineering for health at the NIH. Conference on "Science and Engineering of the Living System," Drexel Institute of Technology, Philadelphia, Pa., March 1968.

______: Engineering for health at the NIH. University of Delaware Symposium Series on Bioengineering. Newark, Del., March 1968.

______: Interviewed by Mr. Peter Hackes, NBC, on the topic of engineering in medicine on the NBC Television network program, "The Today Show," Washington, D. C., March 1968.

______: Biomedical engineering at the NIH. University of Wisconsin, Madison, Wis., and Marquette University, Milwaukee, Wis., April 1968.

______: Opportunities for new bioengineering inventions. Aerospace Industrial Life Sciences Association, Miami, Florida, May 1968.

Peterson, J. I.: Artificial organs. Biology classes of Wakefield High School, Arlington, Va., in observance of Science Day, April 1, 1968.

Pettitt, R.: Careers in biomedical engineering. Engineering students of Rensselaer Polytechnic Institute, Troy, N. Y., May 1968.

Riggle, G. C.: The laser as a tool for medical research. Washington Section, IEEE, Washington, D. C., Oct. 1967.

______: Bio-physical effects of laser radiation. NCI Grand Rounds Program, Clinical Center Auditorium, NIH, Bethesda, Md., Oct. 1967.

______: A team approach toward solving bioengineering problems. Combined seminar with University of Vermont College of Medicine and College of Technology, Burlington, Vt., May 1968.

______: The laser as a tool for medical research. State meeting of Vermont Society of Professional Engineers, Burlington, Vt., May 1968.

Turner, M. C.: The engineering aspects of heart assist devices. Surgical Grand Rounds, University of Pennsylvania Hospital, Philadelphia, Pa., March 1968.

______: (1) An environmental test kit for medical care facilities. (2) An implantable roller pump for cardiac assistance. Third Annual Joint Meeting, The Clinical Society and the Commissioned Officers Association of the U. S. Public Health Service, San Francisco, Calif., March 1968.

Serial No. DRS-BEIB-1

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Mathematical Analysis of Pharmacokinetics - Cancer Chemotherapy

Previous Serial Number: None

Principal Investigators: Robert L. Dedrick, Kenneth B. Bischoff

Other Investigators: David P. Rall, Daniel S. Zaharko, Vincent T. Oliverio

Cooperating Units: EXT-NCI, LCP-NCI

Man Years:

Total:	.3
Professional:	.3
Others:	.0

Project Description:

Objective: To extrapolate results obtained with small animals to rational therapeutic regimens in man.

Methods Employed: Appropriate mathematical models will be developed. Resulting equations will be solved numerically on a digital computer if required by their complexity. *In vitro* and *in vivo* studies will be performed to obtain necessary missing information.

Significance to Biomedical Research and the Program of the Institute: One of the major obstacles to progress in cancer chemotherapy is the inability to extrapolate reliably from results obtained with small animals to regimens for the treatment of cancer in man. A theoretical base to permit such extrapolation and to indicate areas in which insufficient information exists is of vital importance.

Proposed Course of Project: Techniques of mathematical modeling of drug distribution kinetics will be applied to cancer chemotherapeutic agents to account for species differences in tissue binding, metabolism, transport, clearance by the kidney, and removal by extrarenal routes. It is anticipated that preliminary work will indicate areas in which data are insufficient and suggest experiments that must be performed or approximations that can be accepted.

Serial No. DRS-BEIB-2
1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Mathematical Analysis of Pharmacokinetics - Effect of Artificial Kidney

Previous Serial Number: DRS-BEIB-3 (1967 - Fixed Bed Processes for Blood Perfusion)

Principal Investigators: Robert L. Dedrick, Kenneth B. Bischoff

Other Investigator: Jerrold Bernstein

Cooperating Unit: LPHAR-NCI (Baltimore)

Man Years:

Total:	.3
Professional:	.3
Other:	.0

Project Description:

Objective: To elucidate the biochemical events that occur in the body during and subsequent to processing of blood in an extracorporeal device.

Methods Employed: A four-compartment mathematical model involving protein binding, lipid solubility, and metabolism was employed to predict barbiturate concentrations in the body as a function of time. The resulting set of nonlinear differential equations was solved numerically on a digital computer and the results were compared with existing data.

Major Findings: Published pharmacokinetic data for thiopental in dog and man are successfully predicted by the model. The results are consistent with the limited clinical data available for removal of pentobarbital in a hemodialyzer or an activated carbon artificial kidney. The observed rebound in plasma concentration subsequent to cessation of perfusion is explained.

Significance to Biomedical Research and the Program of the Institute: The principal area of kinetic investigation reported in the artificial kidney literature has been the performance of the device. Very little information is available on the events that occur in the body during treatment of blood in an extracorporeal circuit. Such information is relevant to a number of important clinical problems including the "disequilibrium syndrome," the physiologic limits to drug, metabolite or poison removal, and the possible use of an artificial kidney as part of a regimen of chemotherapy.

Proposed Course of Project: It is anticipated that increasing emphasis will be placed on comparative pharmacology of cancer chemotherapeutic agents.

Publications:

Bischoff, K. B. and Dedrick, R. L.: Pharmacokinetics of artificial kidney therapy for poisons. *Proc. Ann. Conf. Eng. Med. Biol.* 9:8.6, Nov. 1967.

_____ and _____: Thiopental pharmacokinetics. *J. Pharm. Sci.* (In press)

Dedrick, R. L. and Bischoff, K. B.: Pharmacokinetics in applications of the artificial kidney. In Dedrick, R. L., Bischoff, K. B., and Leonard, E. F. (Eds.): *The artificial Kidney*. *Chem. Eng. Prog. Symposium, Ser. No. 84*, American Institute of Chemical Engineers, 345 East 47 Street, N. Y., N. Y. 10017, 1968, 64:32-44.

Serial No. DRS-BEIB-3
1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Segmented Polyurethane

Previous Serial Number: DRS-BEIB-1 (1967 - Heart Assist Pump)

Principal Investigator: John W. Boretos

Other Investigators: Don E. Detmer, Frank R. Wagner, Nina S. Braunwald

Cooperating Units: SB-NHI, National Bureau of Standards

Man Years:

Total:	.65
Professional:	.40
Other:	.25

Project Description:

Objective: To conduct research on segmented polyurethane directed toward evaluating its chemical and physico-mechanical properties. In addition, modifications of the polymer will be investigated to enhance its utilization for biomedical applications.

Methods Employed: Several specific areas of investigation are

1. Long-term implants - hydrolytic effects

2. Permeability

3. Particle fragmentation in heart pump sets

4. Polymer modifications

Major Findings: Four-month implants have shown no obvious changes in tensile strength. Further studies are designed to observe hydrolytic stability for periods up to at least two years.

Significance to Biomedical Research and the Program of the Institute: A stable elastomer with high strength properties and physiological compatibility is needed for clinical prostheses.

Proposed Course of Project: Continuation of the proposed evaluation work with the manufacturer of the basic polymer to make it available to the scientific community.

Publications:

Boretos, J. W. and Pierce, W. S.: Segmented polyurethane: A polyether polymer. An initial evaluation for biomedical applications. J. of Biomed. Materials Res. (In press)

_____ and _____: Segmented polyurethane: A new elastomer for biomedical applications. Science 158:1481-1482, Dec. 16, 1967.

Serial No. DRS-BEIB-4
1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Myocardial Infarction Research Unit Instrumentation and Data Acquisition Systems

Previous Serial Number: None

Principal Investigators: Robert J. Pettitt, Gerald S. Cohen

Other Investigators: Peter L. Frommer

Cooperating Unit: MI-NHI

Man Years:

Total:	2.5
Professional:	2.0
Others:	.5

Project Description:

Objective: To improve methods for intensive patient study and coronary care via design and development of new instrumentation systems.

Methods Employed: Collaboration with NHI-MI program office and staff of Myocardial Infarction Research Unit (MIRU) centers on systems analysis and design of monitoring and control methods. Research and experimentation on new instrumentation techniques.

Major Findings: Design and technical specifications for the analog instrumentation and data acquisition system at the Massachusetts General Hospital have been completed. Research has produced several promising new techniques for data handling and cardiotachometry.

Significance to Biomedical Research and the Program of the Institute: Advancements in analog instrumentation and data acquisition systems are essential to the general problem of health research and patient care.

Proposed Course of Project: Continued consultative support to the MIRU program office and to the MIRU centers with significant responsibility for technical aspects of the instrumentation system at the Massachusetts General Hospital. Research will continue on improved coronary care unit monitoring equipment.

Serial No. DRS-BEIB-5
1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Rat Identification System

Previous Serial Number: None

Principal Investigator: Walter S. Friauf

Other Investigator: Horace E. Cascio

Cooperating Unit: TD, NIMH

Man Years:

Total:	1.2
Professional:	1.2
Others:	.0

Project Description:

Objective: To identify individual rats out of a group of 500, at various points in a system.

Methods Employed: Rats will be identified as they pass through portals at test stations and other points in the system. Each rat will have a passive resonant implant which is excited at the portal. The period of the ringing frequency is sensed and used to identify the rat.

Major Findings: Prototype construction has verified the adequacy of the basic approach. Further effort will go into refining the design to allow the desired group size.

Significance to Biomedical Research and the Program of the Institute: This system will facilitate psychological studies where individual traits are important.

Proposed Course of Project: Initial operation with 2 portals and 16 rats is planned for June 1968, with real time interface to a computer for data logging. Then the number of rats and portals will be expanded. Later, real time use of the identification to program test conditions is contemplated.

Serial No. DRS-BEIB-6
1. Biomedical Engineering and
Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Artificial Heart Assist System

Previous Serial Number: DRS-BEIB-1 (1967 - Heart Assist Pump)

Principal Investigator: Marshall C. Turner

Other Investigators: Glenn Rahmoeller, George A. Simon, Lester Goodman

Cooperating Unit: None

Man Years:

Total:	.7
Professional:	.6
Others:	.1

Project Description:

Objective: Refinement of the roller pump system used in previous animal ventricular assistance with success.

Methods Employed: Fabrication and laboratory testing of design improvements, with particular attention to power sources, bearing lubrication, and other mechanical features.

Major Findings: Reliable operation for periods greater than one month has been achieved. A prototype for clinical use has been developed.

Significance to Biomedical Research and the Program of the Institute: An implantable roller pump for long-term *in vivo* use to investigate many aspects of cardiovascular response to assist devices is essential to progress of research on artificial organs.

Proposed Course of Project: A second series of calf implants, using the refined pump, is planned. Design work will continue on this and prototype clinical pumps.

Serial No. DRS-BEIB-7
1. Biomedical Engineering and
   Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Automated Serological Scanner System

Previous Serial Number: None

Principal Investigator: Courtney Mudd

Other Investigators: George A. Simon, Andrew J. Vargosko

Cooperating Unit: CP-CC

Man Years:

Total:	1.
Professional:	1.
Others:	0.

Project Description:

Objective: To develop a system for optical determination of the end-point titration in a hemagglutination (or HI) and complement fixation tests and store data for subsequent processing.

Methods Employed: Photodiodes measure light transmitted through each of 96 cells in test trays. Light level differences between positive and negative tests are electrically sensed and converted into binary form and punched onto a preassigned location on a standard IBM card.

Major Findings: The approach works well for the hemagglutination and HI tests with a preliminary mock-up reading approximately 90% of the tests correctly. The complement fixation test has not been implemented. Most incorrect readings are due to "slippage" of the red cells and "partials" which are neither positive nor negative but are usually read as positive.

Significance to Biomedical Research and the Program of the Institute: The method is capable of significantly improving accuracy and speed over traditional manual techniques.

Proposed Course of Project: Construct a preliminary model and evaluate its use and accuracy in the laboratory.

Serial No. DRS-BEIB-8
1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Physical Correlates of Animal Colony Behavior

Previous Serial Number: None

Principal Investigators: James E. Mitchell, George A. Simon

Other Investigator: John B. Calhoun

Cooperating Unit: LP-NIMH

Man Years:

Total:	.4
Professional:	.3
Others:	.1

Project Description:

Objective: Develop data acquisition systems to monitor certain behavioral aspects of a large (500) rat colony and seek refined mathematical models of social behavior.

Methods Employed: Temporal and spatial monitoring of animal location and movement patterns together with automatic manipulation and registration of task-reward situations.

Major Findings: Prototype location and movement monitors are completed and are under evaluation. Prototype nesting and feeding station monitors are under construction.

Significance to Biomedical Research and the Program of the Institute: Experimental evaluation and verification of theoretical models of animal behavior are necessary to further understanding of human social phenomena.

Proposed Course of Project: This particular project is an early phase of a long-term research project requiring innovation and refinement of a series of measurement and analysis techniques.

Serial No. DRS-BEIB-9
1. Biomedical Engineering and Instrumentation Branch
2. Office of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Automated Amino Acid Analysis

Previous Serial Number: None

Principal Investigator: John I. Peterson

Other Investigator: Erhard Gross

Cooperating Unit: LC-NIAMD

Man Years:

Total:	.7
Professional:	.7
Others:	.0

Project Description:

Objective: To develop an automated amino acid analysis instrument, particularly an automatic sample introduction system.

Methods Employed: Mechanical and chemical engineering design and testing of methods on a prototype instrument.

Major Findings: Two methods for automatic sample introduction have been successfully developed and design of an automated instrument completed.

Significance to Biomedical Research and the Program of the Institute: Automation of amino acid analysis will result in a considerable saving of laboratory manpower and expansion of capacity for routine sample handling.

Proposed Course of Project: Construction and thorough evaluation of instrument based on our designs, with subsequent extension to related laboratory procedures.

Serial No. DRS-BEIB-10
1. Biomedical Engineering and Instrumentation Branch
2. Office of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Automated Sample Combustion System

Previous Serial Number: DRS-BEIB-9 (1967)

Principal Investigator: John I. Peterson

Other Investigators: Seymour Perry, Sidney Siegel

Cooperating Units: MB-NCI, RR-NICHD

Man Years:

Total:	.6
Professional:	.6
Others:	.0

Project Description:

Objective: The development of an automated system for preparation of samples for radiotracer scintillation analysis, using oxygen combustion.

Methods Employed: Experimental combustion techniques based upon extensions of the classic microanalytical combustion method.

Major Findings: The system has been completed for tritium analysis and is capable of treating samples up to 500 mg at a rate of 20 samples per hour with an error of ± 1% and tritium recovery of 96%.

Significance to Biomedical Research and the Program of the Institute: This development can significantly reduce the time and cost involved in preparation of biological samples for radiotracer analysis.

Proposed Course of Project: The collection system for CO_2 must be perfected to allow use of the system for C^{14} labelled samples and will be followed by thorough evaluation and extension to related laboratory procedures.

Serial No. DRS-BEIB-11
1. Biomedical Engineering and
Instrumentation Branch
2. Office of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Utility of Lasers in Biological Research and Clinical Applications

Previous Serial Number: DRS-BEIB-6 (1967)

Principal Investigators: Grant C. Riggle, Alfred S. Ketcham

Other Investigators: Woodrow F. Stotler, Robert C. Hoye

Cooperating Unit: SB-NCI

Man Years:

Total:	1.25
Professional:	.75
Others:	.50

Project Description:

Objective: To regulate and quantify laser energy and its effects on biological tissue as in several fields of medical research investigation. Emphasis is on cancer and neurology.

Methods Employed: Development of an extremely reliable, high energy system with controllable energy levels and pulse lengths and evaluation of effects by physical and physiological measures.

Major Findings: Distribution density and rate of delivery were significant factors in improving the destruction rate while reducing the dosage level. Marked improvement has been achieved in the predictability of tumor destruction using smaller dosage levels. High power laser action has produced insignificant effects and no further studies are contemplated at this time.

Significance to Biomedical Research and the Program of the Institute: Light energy has considerable promise for biomedical research, surgery, and therapy. Considerable fundamental and applied research and development is required to exploit its potential.

Proposed Course of Project:

1. A clinical unit is now functioning. Selected subjects from time to time will be treated to determine results of a controlled energy.

2. Investigation of results on human cancers with systems research on improving and overcoming problems related to patient treatment needs.

3. Continuation on the determination of biological effects resulting from a variety of laser wavelengths.

4. Development of systems for investigation of effects at cellular levels; secondary tumor regressions; and measurement of physical forces resulting from laser action.

Summary of Branch Activities July 1, 1967, through June 30, 1968

LIBRARY BRANCH

Jess A. Martin, Chief

I. SUMMARY

The NIH Library moved into a new facility providing more than twice as much total space, 42,500 square feet, and accommodating twice as many patrons as the former Library. The move was completed on April 29. Special sound reducing features in the new facility include a silent paging system and carpet in the Reading Room.

A journal collection evaluation was conducted by 75 scientists representing various subject specialties. A listing of periodical titles recommended for addition to the collection has been compiled. A list of titles recommended for deletion is in process.

The fourth year of the library internship program began in August. Two interns are given rotating work assignments to gain experience while making contributions to the service program. The NIH library internship program is one of only six now in existence in this country.

Automation within the Library Branch was concentrated in two areas: businesslike transactions, such as serials recording and acquisitions, and publications. Automation of circulation procedures, including overdues, was given some attention and will receive greater emphasis during the coming year.

Training of the staff was stressed. Courses in automation, systems design, psychology, and foreign languages were taken by professional staff members, with library principles and organization being studied by library technicians.

The Branch Chief announced his resignation effective July 15, 1968, to accept appointments as Director, Health Sciences Library and Associate Professor of Medical Librarianship at Temple University.

II. BRANCH PROGRAMS

A. Objectives

The primary mission of the Library Branch is to operate an efficient, comprehensive library in support of research and administrative programs. Activities of the Library include the acquisition, processing, maintenance, and circulation of materials; operation of a photocopying service; provision of informational, reference, consulting, and bibliographical assistance; and provision of a translating service for foreign scientific literature. To fulfill its mission, the Library is responsive to the changing literature needs of the NIH investigator and is knowledgeable of the current manual and machine methods of handling scientific information.

B. Current Programs

Readers Services. Readers services for the NIH staff include reference assistance, circulation and maintenance of printed matter and micromaterials, photocopying, and translation.

The reference staff also compiles short reference lists and performs comprehensive literature searches as requested by NIH investigators. In order to answer the multitude of inquiries for specific information, reference librarians endeavor to keep abreast of the biomedical activities of NIH and other research institutions. They are also responsible for selecting new materials for the library collection.

The Circulation Unit, through surveillance and inventory of the collection, maintains the materials in a manner to encourage easier access for clientele. An extensive photocopy service within the Circulation Unit allows greater use of library literature. Another activity of this Unit, the interlibrary loan program, makes available books and journals not found in the NIH Library.

Still another important readers' service offered is the translation of foreign scientific literature. Ten foreign languages are handled by six staff translators. Other languages are translated by contract.

Technical Services. Technical Services include the acquisition of books, journals, technical reports, and micromaterials needed to support the research efforts of NIH scientists and the processing of these materials for use. Certain automated procedures now being implemented will reduce ordering and processing delays. A gift and exchange program permits valuable materials to be added to the collection at little cost to the Library.

Bibliographical Services. MEDLARS requests for NIH scientists are formulated by experienced searchers of the Bibliographical Services Section. Other programs of mechanized information handling are being planned and coordinated with existing programs at the Division of Computer Research and Technology, National Library of Medicine, Library of Congress, and other agencies. Responsibility for assisting the Institutes with the organization and development of satellite libraries rests with Bibliographical Services. Other functions include collection evaluation and user studies.

C. Program Progress and Accomplishments

The move of equipment, supplies, and personnel to the new library facility located on the first and first basement levels of the Clinical Center was begun on April 19 and completed on April 29. During the move limited service was provided at both the old and new locations.

The new facility features sound reducers in the form of carpeted floors, architectural curtains, and a silent paging system.

The automation programs of the Library continued with the coding of the history statement for periodicals being completed. Several library publications were computerized for the first time. The NIH Library Booklist, produced by the computer, was distributed in September with its frequency changed in January from bimonthly to monthly. Recent Translations and Translations Index, Supplement IV, 1967 were also computer produced. In an attempt to speed the up-dating of the In-Process List, a second keypunch was leased.

A study of the automation possibilities within the Circulation Unit as they relate to charging books and overdues was conducted by the Systems Analyst. Systems design has been delayed pending the gathering of additional data.

Training of the library staff involved coursework in systems concepts, design, facilities and analysis, psychology, and foreign languages. Library Technicians on the staff took courses entitled, "Introduction to Library Service," and "Principles of Library Organization." One staff member was provided in-house training as a reference librarian while actually serving as a circulation librarian.

The fourth year of the library internship program began in August, with the arrival of two interns. They are provided an opportunity to gain work experience in a research library while making a substantial contribution to its service program. Three of the first five interns elected to remain on the staff of the NIH Library. An internship brochure was distributed by the NIH Library to accredited library schools around the country.

Readers Services

Effective September 30, the responsibility for supervising the Library on weekends was transferred to five professional librarians of the Readers Services Section. Coverage for the Library is provided during the hours 8:30 a.m. to 12 midnight, seven days per week.

Photocopying Service. Xerox 720 and Xerox 914 photocopiers are used to fill urgent photocopy requests of 20 pages or less. Longer articles are photographed, processed, and then printed by the Xerox Copyflo. The faster copier (Xerox 720) will improve a service that has become the most heavily used of all library services. Approximately 75,000 pages per month are being copied for NIH scientists. An NIH photocopy operator continues to serve one-half time at the National Library of Medicine to assist in a program to provide one-day processing of the NIH interlibrary loan requests. Almost 80 percent of the requested articles were photocopied and returned to the NIH Library the same day. Photocopy film, formerly processed by a commercial firm, is now processed by the National Library of Medicine in an attempt to save time.

Circulation. A total of 39,000 books and journals were circulated during FY 1968. Approximately 7,500 were loaned, and 8,500 were borrowed from other libraries. Approximately 5,200 copies of translations were provided to other libraries.

The Borrower's File at the Circulation Desk was discontinued. Since some NIH groups did not clear through the Library, the cost of maintaining the file was not justified.

A study of the TWX Communication System in Libraries was conducted, and it appears that the system should be installed to speed the Library's interlibrary loan transactions.

Reference Service. Because emphasis is placed on supplying quick response to reference questions asked by phone or in person, reference librarians regularly scan the current scientific literature to keep abreast of the latest publications. The book and journal selections program is another responsibility of reference librarians. Included in this is a continuing search of journals, publishers' catalogs, national book catalogs, and announcements for current publications needed for the collection.

Translating. The first automated supplement to the NIH Translations Index was compiled and appeared as Supplement IV. The supplement again includes a subject index and a list of journal abbreviations. Each year approximately 500 articles are translated, with 85 of these being handled by contractors. Oral translations for the year consumed 1400 man-hours. Tape recordings of translations were provided on request.

Technical Services

Acquisitions and Cataloging. During this 12-month reporting period, the Library's collection was strengthened by the addition of 4,500 new books and by the receipt of 500 books through gift and exchange. For FY 1968, the Library placed subscriptions to more than 2,227 journal titles and received an additional 800 as gifts or on exchange.

The Acquisitions Unit began placing two-year, rather than one-year, subscriptions to several journal titles--a practice which reduces costs significantly.

Made available for the first time was an alphabetical list of periodicals which are on standing order. The list simplifies the book selection procedure presently being used.

Bibliographical Services

During the fiscal year 434 MEDLARS requests were handled by the Bibliographical Services Section. Most of the requests for MEDLARS services are now being formulated by personnel of the NIH Library rather than being sent directly to NLM.

Keypunching of MEDLARS searches was begun at the NIH Library with the result that searches are now sent more quickly to the NLM computer. The new arrangement ensures faster service for NIH scientists.

A survey of the entire collection of the library is currently underway. Seventy-five scientists were asked to survey certain subject areas. Their work has been completed. A tabulation of their recommendations is now being compiled.

Five Institutes and Divisions are now receiving the monthly alerting service entitled, Information from the NIH Library. Distribution to all I/D's is being planned.

D. Problems

Deterioration of filmed translations appears to be the result of improper storage. Advice of Medical Arts and Photography Branch has been sought. Journal renewals placed with the Veterans Administration have not been handled effectively during FY 1968. Determination needs to be made whether VA should be retained as a primary vendor.

A careful re-evaluation of the role of the Library Committee should be conducted and new guidelines developed.

E. Program Plans

Study of other information retrieval systems that can be adapted for use by the NIH Library will continue.

The Systems Analyst, with assistance from other staff members, will automate the circulation procedures and give special emphasis to the time-consuming recall of overdues.

Evaluation of the collection will continue, with NIH scientists providing expertise and subject knowledge that are invaluable to this type of program.

A fifth medical library internship program conducted by the NIH Library is planned for 1968/69, beginning in August.

F. Publications

Martin, J. A. What Happens to Medical Library Interns? Bulletin of the Medical Library Association, Vol. 55: October 1967.

Martin, J. A. Planning the New NIH Research Library. Special Libraries Vol. 59: January 1968.

National Institutes of Health Library: NIH Library Booklist. Bethesda, Md., monthly.

National Institutes of Health Library: Periodicals Currently Received in the NIH Library, 1967. U. S. Dept. of Health, Education, and Welfare, Public Health Service Publ. No. 1313. Washington, D. C., U. S. Govt. Print. Off., 1967.

National Institutes of Health Library: Recent Translations, a Selected List. Bethesda, Md., monthly.

National Institutes of Health Library: Index of Translations, Supplement IV. Washington, D. C., U. S. Govt. Print. Off., 1968.

National Institutes of Health. NIH Library Guide. Bethesda, Md. 1968.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1967 through June 30, 1968

MEDICAL ARTS AND PHOTOGRAPHY BRANCH Charles C. Shinn, Chief

I. SUMMARY

The Medical Arts and Photography Branch provides the knowledge, skills, and techniques for visually communicating research information, for preserving observations of NIH scientists, for recording research activity, and for preparing effective research reports.

Professional designers provide not only visual presentations such as motion pictures, slides, exhibits and publications, but counsel and advice on selection of appropriate media and effective methods for achieving desired results.

In the first half of the year, the Branch operated without a full-time Chief. The Administrative Officer position became vacant, and the Branch continued to lose key employees through transfers and retirement. In December 1967, Mr. Charles C. Shinn reported for duty as Branch Chief to begin a period of orientation and assumption of full-time leadership.

In FY 1968, the Branch handled a greater volume of work than in previous years. For example, 26,600 requisitions for work were handled as compared to 22,600 in FY 1967, the previous high. It is noteworthy that the total Branch staff is the same today as it was in 1965, while work requests processed were up 61 percent in 1968 over 1965. Part of the increased productivity was achieved through use of new automatic processing equipment. Increased use of outside contracting and overtime also helped. During the latter part of the year, several policies and standardized work procedures were instituted to further improve production. In addition, limited shifting of personnel and the recruitment of young artists for temporary employment and for work-study arrangements were begun. A long-range program including training and work evaluation was started.

Plans were completed for moving the Branch to its new central location in the Library Annex of the Clinical Center. This centralization of Branch activities should greatly benefit all of the major programs. More efficient management and administration, simplified work reception, measurement, and work flow, centralized quality control, spot checking of work in process, as well as day-to-day design and performance reviews will soon be possible. To this end a central Branch conference/presentation/planning room is contemplated. A convenience to clients whose work involves several activities of the Branch also will accrue.

A task force on centralized work control and workflow analysis was formed late in FY 1968 with final recommendations due prior to the move to new quarters scheduled for late August 1968.

A number of important management changes were made during the year.

II. BRANCH PROGRAMS

A. Objectives

The objective of the Branch is to provide a central, high-quality source of design, art, and photographic services in support of research programs at NIH. The Branch provides a central capability for rapidly responding to individual research scientist needs, for recording on-going research activity, and for reporting research findings in any of the visual media to both professional and public audiences.

It is also the objective of the Branch in meeting NIH research program needs, to provide in-house services on a professional basis competitive with commercially obtainable services at the lowest possible cost, to do necessary research and development of tools and techniques to improve art and photographic service, and to develop specialized capabilities, particularly in still and motion picture photography and in medical art and model making, tailored to NIH needs.

The Branch monitors procurement of art and photographic services by outside contract, serving as technical adviser and counsellor in obtaining the needed additional services at the lowest cost consistent with high quality.

B. Current Programs

The programs of the Branch include still and motion picture photography including photomacrography, photomicrography, time-lapse and high-speed cinematography, general photography, and related laboratory services; visual arts production including publications design and general graphics; visual aids including slides, vu-graphs, and other projectables; animation art work; technical, general, and medical illustration; exhibit design; statistical drafting; display charts; and medical models.

C. Program Progress and Accomplishments

In FY 1968, the Branch handled a greater volume of work than in any previous year. For example, 26,600 requisitions for work were processed as compared to 22,600 in FY 1967, the previous high mark. Approximately 87,000 ft. of motion picture film was exposed as compared to 70,000 in 1967 and 30,000 in 1966. Both major and minor motion picture production increased. Approximately 190,000 photographic prints were processed; approximately 80,000 2x2 color slides were made. Lantern slide production decreased to about 10,000, being gradually replaced by the 2x2 size. The switch to the more popular size also resulted in some material savings.

Photographic contract work reached a new high as did outside contracting for exhibits, art work, and statistical drafting. For example, outside contract services for art work and exhibits processed by the Branch reached $75,000; $31,000 was spent on procuring outside charts, tables, and statistical drafting. Money spent outside on exhibits is primarily for construction. This is more feasible and economical and should continue.

However, a greater in-house capability for handling design, art work, and statistical drafting could save money, especially during peak periods. A study of contract work in this area during a peak period from February through April 1968 revealed that outside contracting cost $14,800. It is estimated that the same work could have been accomplished in-house at about one-third the cost.

Perhaps the most progress was made in the motion picture program. A high-speed motion picture capability became fully operational and already has satisfied a number of requests for services. Primary application was in pulse laser impact investigations. It centers around a Hycam 400 ft. camera. Modifications to equipment increased our capability from 9,000 pictures per second for only 0.75 seconds to 11,000 pictures per second for a period of 2.175 seconds. This important improvement produced a higher percentage of successful photography because of the longer, workable period of time and greater latitude. High-speed photography is expected to increase as numerous investigators have expressed enthusiasm about demonstrated capabilities of the system.

As a result of experimentation and development of the high-speed camera, an original prototype high-speed camera exposure computer was designed. This unique device, based on a Polaroid picture exposure, greatly simplifies and speeds up calculations to obtain proper exposure for high-speed cameras. Clarification of patent possibilities for this device has been requested.

A portable time lapse cinephotomicrography service was established. It is now possible for research investigators to obtain a complete setup for time lapse cinephotomicroscopy using the researcher's laboratory photomicroscope. MAPB provides instruction in its use as needed. Upon completion of projects, the camera equipment is returned to MAPB for subsequent release to other investigators.

The use of a teleprompter was instituted. It proved invaluable in achieving satisfactory synchronous sound photography.

The Steenbeck editing system became fully operational. This has speeded up and improved the whole film editing process.

Interrelationships with clients during pre-production planning and writing of motion picture research reports were improved. The sketchy, disoriented approach that handicapped the film program in previous years has been drastically changed. Further education of clients to motion picture production requirements hopefully will reduce the problem.

Following is a list of the more significant motion pictures and film strips completed during the past year:

1. "Case Studies of Oral and Pharyngeal Form and Function". This two-part motion picture research report was used as an integral part of an award-winning NIDR exhibit. Copies were prepared in 8mm sound, color for use in endless loop cartridges.

2. "Impulse Propagation in a Nerve Fiber". This research report for NINDB employed conventional and computer animation. It is in 16mm color, sound, 20 minutes in length.

3. "Extended Resection of Basal Cell Carcinoma of the Scalp, Brain and Face". This 16mm sound, color research report for NCI is 20½ minutes in length.

4. "Artificial Kidney". This public information film for NIAMD is 16mm sound, color, 14½ minutes in length.

5. "Surgical Correction of Vascular Obstruction of Superior Infundibulum". This research report is 16mm sound, color, 22 minutes in length.

6. "Left Ventricular Bypass with a Roller Pump", is a 16mm sound, color research report, 11 minutes in length.

7. "Patient Memory Tests". This title was produced as two films: one sound, one silent. The films are for use by the Geriatric Section, NICHD. Both films are black and white and run 16 minutes each.

8. Two lengthy 35mm black and white film strips were prepared for NIMH to be used in visual tests. They required critical tone control and unusual precision in the preparation of art work and in final photography.

9. "Laser Surgery of Melanoma on Mouse". This high speed footage in color was successfully accomplished at 11,000 frames per second.

The development of a life-size, flexible plastic eye model was completed. This project, over two years in process, represents the combined efforts of many personnel in the Branch. Research and development progressed from a rigid model to a final flexible model demonstrating the entire normal fundus. The artificial eye has been used at NIH for demonstrating ophthalmic instruments and techniques. Trials indicate that it will be useful for practice in direct and indirect opthalmoscopy, fundus photography, slit-lamp examination, and many experimental setups for laboratory work. It will eliminate the need for human subjects in some cases.

The production of medical models and moulages increased, reflecting changing Institute programs and development of increased expertise in Branch services. Improvements were made in the jeltrate casting procedure to give smoother, more flexible molds that produce perfect casts without loss of detail.

Significant contributions in clarifying surgical technique and procedure in motion pictures were made by adapting medical illustration to the motion picture medium. Medical illustrations clarified and oriented the audience to changing positions of camera and patient. A significant example was in the NCI motion picture "Extended Resection of Basal Cell Carcinoma of the Scalp, Brain and Face".

Statistical drafting, general graphics and art work, exhibits, publications, animation art and art work for slides, charts and tables to illustrate scientific papers, all reached new, high levels of production. In addition, work processed through the Branch to outside contractors reached all time high levels. The ability to meet short deadlines improved--sometimes at the cost of quality.

A number of pieces of new equipment and invaluable work tools were added. For example, ozalid diazo process equipment was added to streamline production of film titles and copy for slides. The process cut the unit cost of titles and certain types of slides. Improvements in technical photography were made, particularly in handling heavy volume of gross specimens illustrating various types of artificial heart valves, effect of materials on living tissue, rejection of materials, valve design, etc.

Specialized methods of photographing immuno-electrophoresis plates in the study of protein reactions was perfected. Photography was scheduled in coordination with research efforts. It served as a laboratory record.

Photomicrography of agar gels showing migration of antibodies was perfected to demonstrate the path and effect of the migration. The photographs served as a basis for laboratory computations.

Ultra violet fluorescent photomicroscopy improved. As a result of increased demand, an additional photomicroscope with accessories for 35mm production was purchased. Further experimentation is under way with high-speed color film and special film processing to photograph living cells at low excitation levels under high magnification and ultra violet radiation.

Overall progress has occurred in coordination of activities among the Sections of the Branch. Regular weekly Section Chief meetings center on this objective. For example, art work for color slides, motion picture animation, titles, large presentation charts, etc., is becoming more carefully coordinated in design stages at inception of assignments. More rapid progress in this area should occur when the Sections are brought together in FY 1969.

Among the more important management improvements made during the year are the following.

1. Consolidated purchase orders for two Sections are now placed at regular intervals. Previously, they were placed individually, at random as needs occurred.

2. Standards were established with the Government Printing Office for NIH signatures on medical illustrations. Samples supplied by the GPO are accepted by MAPB as a general guide; exceptions are to be made on individual basis.

3. A policy for central clearance of publications design and art work was established within the Branch.

4. A single, responsible liaison officer was designated to represent the Branch on all printing problems with the NIH Printing and Reproduction

Section and with the Government Printing Office on matters of design.

5. A new photographic release procedure and form were developed and established.

6. A policy was established in the Branch for clearance of all art work for use in motion pictures and television.

7. A clearance procedure for both motion picture research recording and motion picture research report productions was established with Scientific Directors of the Institutes and Divisions.

8. Design and production of 30 x 40 presentation charts, particularly those for Congressional hearings, were standardized for more rapid, effective production.

9. A unified, improved reporting system for Section activity was developed within the Branch.

10. Basic statistical charts measuring production were established and are updated regularly.

11. Art work for 2x2 slides, 3-1/4 inch slides, television and motion pictures was standardized as to original size and scale.

12. All accumulated motion picture footage at NIH was sent to the Federal Records Center for archiving, subject to 24-hour retrieval notice.

D. Problems

The loss of personnel and the difficulty in finding replacements is a continuing problem. This shortage of qualified medical illustrators, top flight graphic designers, and scientifically oriented photographers and photo laboratory technicians still exists.

A relatively low pay structure at NIH, coupled with the need to attract personnel away from the center of commercial activity in mid-city, contributes to the handicap in competing for the limited number of available candidates.

Much can be done to re-orient, upgrade, and structure positions now in the Branch. On the positive side, appointment of a well-qualified Motion Picture Section Chief at higher pay is directly responsible for the surge forward in the motion picture program.

Over the long range, specific positions, particularly in shortage categories, should be upgraded to attract better quality personnel, at the same time providing an infusion of new, younger talent.

A high proportion of the staff is approaching retirement age or years in which the pace can be expected normally to slow. With increased technical development and more sophisticated equipment, a continuing effort to recruit new, young talent with emphasis on formal education in the arts and on technical training is necessary.

Another problem is preventive maintenance and routine replacement of worn equipment. Commercial resources for maintenance have not proved adequate, nor is there a plan for preventive maintenance, identification of obsolescence, and scheduled replacement. During the coming year, a program will be developed.

Analysis of funds spent on work sent to outside contractors reveals that they well exceed costs of work done in-house. At the same time, there is a direct cost and loss of effort in handling this work that has not been taken adequately into account in measuring work produced or in staffing.

More effective contract work handling and monitoring by the Branch to improve quality and to identify better contractors will produce consistently higher results. Greater in-house capability in peak periods needs to be developed. Preplanned use of temporary employees and a modest increase in permanent staff seems to be the most promising solution. Proposals along these lines are being developed.

Although the new centralized Branch space offers many previously defined advantages, it also presents serious deficiencies. Some can now be identified and corrected--for example, the lack of adequate sound proofing and control in the motion picture studio.

The effect on morale and performance of creative artists, designers, and others working continuously in windowless, subterranean space may be a problem.

E. Program Plans

The coordination of work by the Branch Sections has improved but still could be better. During the coming year, results of the task force on work flow and work control, coupled with the move into the new quarters, will provide opportunity to consistently coordinate talent, training, development, and performance of personnel.

A modest reorganization is anticipated along broad functional lines. It is needed to capitalize upon existing skills and talents, to cope with increased work loads, to take advantage of opportunities provided by the new central space, to more carefully define duties and measure performance, to improve supervision, and to attract the best talent available.

Until now the Branch has produced motion pictures with portable sound equipment. In the coming year, the sound studio in the new Branch space will be equipped with a quality sound recording facility. An engineering study is now underway which will result in sound proofing recommendations and identification of appropriate sound recording equipment, a major contribution to motion picture quality.

It is hoped that much of the effort can be saved that is now diffused through NIH Institutes and Divisions where individual draftsmen, photographers, and practitioners are isolated. At present, the Branch finds itself patching much inadequate work done elsewhere to reach minimum reproduction requirements.

Finally, a coordinated effort will be made to improve attitudes, develop more professional behavior, and establish identity as experts in visual communication. The result should be a more broadly based, better integrated service with objectives more critically identified.

Over the long run, it is hoped that a higher standard of performance will emerge.

LIBRARY
NIH
Amazing Research.
Amazing Help.

http://nihlibrary.nih.gov

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

NIH LIBRARY
4 0107 9614

NIH LIBRARY
3 1496 00179 3051